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ANNALS OF TROPICAL MEDICINE  
AND PARASITOLOGY



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( THE UNIVERSITY OF LIVERPOOL )

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ANNALS  
OF  
TROPICAL MEDICINE AND  
PARASITOLOGY

ISSUED BY THE  
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Edited by

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Ernst. Evans.

# PRESENTATION OF THE MARY KINGSLEY MEDAL

TO

DR. GRIFFITH EVANS

The North Wales Branch of the British Medical Association on 14th December, 1917, gave a luncheon at the Imperial Hotel, Colwyn Bay, in honour of Griffith Evans, M.D., C.M. (McGill), M.R.C.V.S., of Brynkinallt, Bangor, on the occasion of a presentation to him of the 'Mary Kingsley Medal for distinguished Scientists who have assisted the cause of Tropical Medicine by original research.'

The Committee of the Liverpool School of Tropical Medicine had unanimously agreed to offer to Dr. Evans the Medal of the School, which was struck in commemoration of the work of the late Miss Mary Kingsley in West Africa.

At the luncheon Dr. H. Drinkwater, of Wrexham, presided, and in proposing his health said that their distinguished guest was the pioneer in the study of Protozoology in connection with infections, and had added something of permanent value to the sum of human knowledge.

Professor J. W. W. Stephens, of the Liverpool School of Tropical Medicine, formally presented the Medal of the School to Dr. Evans, and also the following address:—

'We, the undersigned members of the Professional Committee of the Liverpool School of Tropical Medicine, desire to offer you our hearty congratulations on the presentation of the Mary Kingsley Medal to you in recognition of your distinguished scientific work. We recall that you were the first to associate trypanosomes with the production of disease, and the specific name of the trypanosome of surra which you discovered will always perpetuate your name in connection with that discovery. All the more honour is due to you also for maintaining the correctness of your view, that the trypanosomes caused the disease surra, in the face of official opinion to the contrary. We trust that in due time we may have the pleasure of honouring you in Liverpool.—We are, yours respectfully, Richard Caton, Chairman; J. W. W. Stephens, Professor of Tropical Medicine; Robert Newstead, Professor of

'Entomology; Warrington Yorke, Professor of Parasitology, 'B. Blacklock.'

Dr. Griffith Evans, in reply, said he felt highly gratified by the honour which had been conferred on him.

He proposed the toast of 'The Liverpool School of Tropical Medicine,' and said that the School had done incalculable work in the cause of the scientific pathology of the tropics.

Professor Stephens, in responding, said that the School was still hard at work, but the new laboratories into which they had proposed to move were at present being used as a military hospital. He hoped soon to be able to welcome Dr. Evans and the members of the Association there.

#### AUTOBIOGRAPHICAL MEMOIR

I was born at Tymawr, near Towyn, Merioneth, 7th August, 1835, being the only son of my parents, Evan and Mary Evans.

Educated at the British School, and by private tuition.

Was for a short time pupil of John Pugh, F.R.C.S., Aberdovey and Towyn, but circumstances diverted me to the R.V.C., London, to qualify for appointment as Veterinary Surgeon in the Army, and I obtained a commission in the Royal Artillery, January, 1860. That was in the Regimental time, before the Departmental system was thought of, and eleven years before the purchasing of combatant commissions was abolished. I mention this to show what social changes I experienced, and to say I have very happy recollections of the old régime.

I went to Canada with troops in the famous S.S. 'Great Eastern,' because of the U.S. Civil War, and was stationed at Montreal, June, 1861. Registered in the Medical Faculty, McGill University, without delay, and graduated M.D., C.M., in 1864. The subject of my graduation thesis was 'Tuberculosis,' giving evidence of its infection, character, and advocating the open-air treatment. Professor Fraser, who had read my thesis, challenged the infection in Convocation, but I maintained my ground by added evidence of my own observation. I continued working there for another year, especially in regional anatomy, surgery, and clinics.

In 1865 I spent two months visiting the Field Hospital of the Northern Army (there I learnt how much better the medical and

surgical cases did in tents than in the best walled hospitals of the period), being the first English Officer allowed to go after the great disaster in 'The Wilderness,' etc.

Afterwards I was stationed at Toronto, when I became acquainted with a charming young man, then beginning his medical study as pupil of one of the leading general practitioners there, now the Regius Professor of Medicine, Oxford—Sir William Osler.

I returned with troops to England, July, 1870, in the Indian Troopship 'The Crocodile,' specially sent on account of Prince Arthur, then a subaltern in the Rifle Brigade, who was returning with his battalion. The Queen's yacht, 'The Victoria and Albert,' came to meet his arrival in the Channel to take him to Osborne, and brought news of war declared by France against Prussia, which was a great surprise to us all.

I went with my battery to Ipswich, where I was stationed for nearly a year, and was most kindly privileged by the Medical Staff of the Infirmary to benefit by their practice. I was there almost every day.

One day a young son of a sergeant in my battery was knocked down in the street by a dog-cart, the wheel of which passed over his head, wounding him severely. He was carried to the Infirmary unconscious. His mother came to me that evening in her distress, begging me to treat him if she brought him home. I persuaded her to leave the boy where he was, promising to see him every day. When I arrived there one day I was told he had tetanus, and there was going to be a meeting to consult *re* treatment, to which I was invited. There had been a remarkable run of tetanus, I forget how many cases, from the mechanical works mostly, and all had proved fatal, though every recognised method of treatment had been adopted. Amputation had been tried in a case of injury to the end of a finger. I was asked to give my opinion. I replied that I regarded the disease as a specific fever, due to some specific cause, and for which there was no known specific remedy. It had to run its course like other specific fevers, and our duty was to keep the patient in the best possible position for self-recovery, that was, to favour as much easy rest as possible, avoid everything that might excite the spasm, keep in a dark silent room, no noise from without or within, give no food of any kind, nor any medicine, but let the patient drink water *ad lib*. No one should go in to see him except

a specially selected nurse and the House Surgeon. They all protested against not giving any medicine of any kind; if the patient died they would blame themselves for neglect. After some conversation, I was asked would I venture the risk if I were responsible for the treatment? I replied, I would without hesitation, with the consent of the parent. They all agreed for me to take charge of the case, the patient remaining in the Infirmary. The mother was called in, the subject was explained to her, the fatality of previous cases, etc., and she expressed her willingness to comply with any treatment I recommended, and promised also for her husband.

*That case recovered.* It is the only case I ever had to treat in man, but I have treated a number of cases in horses on the same principle, and all recovered.

In the autumn of 1870, I married Catherine, only child of John Jones, M.R.C.S., who had an extensive country practice at Llanfaircaerinion, Montgomeryshire. I was tempted to settle there with him, but was too fond of the roving military life.

In 1871, I exchanged from the Royal Artillery to the Army Service Corps, and was posted at Woolwich, with a prospect of remaining there several years. It suited my fondness to prosecute my medical studies, and I arranged to work through a post-graduate course of Practical Histology and Experimental Physiology at King's College, London; also a six months' course of lectures and clinics at the Royal Ophthalmic Hospital, Moorfields, where I was fortunate in having the friendship of Jonathan Hutchinson, Senior, who most kindly invited me to his clinics at the London Hospital, where I learnt much.

You ask 'especially' for 'some fuller details of my discovery of the *Trypanosoma evansi* than one finds in books.' Perhaps I had better tell you first how I became prepared to find it, and to try not to be too prolix.

Microscopy was my hobby since my earliest student days. I had kept myself informed of Pasteur's investigations and discoveries of pathogenic bacteria, and was deeply impressed with the conviction that a new door was opened for great developments in medical science. When I was sent to India in November, 1877, I provided myself with a portable microstand, with the best lenses I could obtain up to  $\frac{1}{12}$ th immersion, with suitable condenser, sub-stage, etc.



On arrival in India, I was sent to Sialkot in the Punjab, to investigate a disease that was endemic, and had been for many years extremely fatal to cavalry and artillery horses there, and at other stations in India. The symptoms varied extremely in each outbreak, according to the organs chiefly affected, respiratory or alimentary in different patients. I proved it to be anthrax fever, by finding the specific bacillus in the living circulating blood of every patient. I officially reported, what surprised me most, that the first change in the blood seen by the microscope was a great increase in the number of the large white corpuscles before I could see a bacillus. I examined the blood regularly every hour from the first symptom of illness, and noted invariably the increasing number of these corpuscles for some time before I could find a bacillus. The bacilli, when they came, appeared to be closer to the white than to the red corpuscles; subsequently the number of the bacilli in each droplet multiplied rapidly, so they could be seen isolated, free from corpuscles. I expressed my conviction that the large granular corpuscles had a very important relation to the bacilli, but I could not think what it was. I repeatedly emphasised my belief that it deserved special investigation. You will notice that was before Metchnikoff discovered them to be phagocytes, as published in 1884. I did not know, in 1878, how to fix and stain microbes in the blood for microscopic observation, so I floundered on, observing what I could.

In August, 1880, I was officially requested to proceed to Dera Ismael Khan, to investigate a disease known as 'Surra,' that had been very fatal to horses and camels of the Punjab Frontier Force for many years. I asked to be furnished with all the reports made upon it by surgeons, human and veterinary. After reading them, I was of opinion it was due to some parasite in the blood, though that was not suggested by anybody else. I expressed that opinion to the head of my Department, and stated that I could not undertake to investigate the disease unless I was fully authorised to kill as many of the patients as I wished in any stage of the disease for examination post mortem; and to make any experiment I might wish to transfer the disease to any healthy animal I would select for the purpose, so that I might know whether it was transferable, and, if so, that I might be able with certainty to study it from its earliest stage onward.

The progress of the disease was notoriously slow, and no one had been able to recognise it until after it had made some progress in wasting and general debility. Strong objections were made to giving the authorisation I requested. The question was ultimately referred to the Lieut.-Governor of the Punjab personally, and after some further cross-firing he decided entirely in my favour. Orders were issued to all concerned to give me every facility.

On arrival at Dera Ismael Khan, I called upon Dr. Haig, Surgeon of the cavalry regiment, and invited him to go with me to examine microscopically the blood I would take from a surra patient. (There was no European veterinary surgeon with the native cavalry.) Fortunately, after I examined the first droplet, I was able to say, 'Look at that, alive with microbes, such as I have never seen before: tell me what they are, if you know.' Dr. Haig did look, and was greatly astonished. He did not know what they were, but because of their great activity and their apparent onslaught upon the red corpuscles he suggested they should be named 'ferox.' That is how I discovered what have been given my name, firstly *Trichomonas evansi*, afterwards called the *Trypanosoma evansi*.

I selected two healthy horses which had not been near a case of surra. I poured the living blood of surra into the stomach of one, and under the skin of another. They sickened, and the special microbe in question swarmed in every droplet of their blood on the sixth day. The experiment was repeated with two other healthy horses, with the same effect. The four developed all the symptoms which were regarded as characteristic of surra.

I found that the blood with the microbes swarming in it when drawn, if set aside in an open or closed vessel to clot and cool, would become clear after twenty or twenty-four hours. I poured such blood into the stomach of a healthy horse, and injected it under the skin of another, with no effect in either case.

I communicated the disease from a horse to a dog and to a bitch, likewise by subcutaneous injection of the blood, and by the stomach. They sickened, and the microbe appeared in their blood. The bitch had a young pup that became affected with the disease by sucking her. I could not account for it otherwise, though I did not find the microbe in her milk. It was necessary to make further experiments carefully to decide that question, but I never had an opportunity.

I do not know whether anyone else experimented in that direction. I reported what I observed for others to continue.

I did not find an increase of white corpuscles in the blood *before* the appearance of the microbe in the cases communicated, as above stated, from horse to horse: but I noticed them in a few hours after, as recorded in my official reports thus:—‘Beside the presence of the parasite, the elements of the blood became abnormal. The first apparent change is an increase in the number of white corpuscles; sometimes one-third or even half the number of corpuscles in the field will be white, and a remarkable increase in the proportion of the *large granular* white corpuscles.’ But the dog and the bitch to which the disease was communicated as above stated had a great increase of the large granular white corpuscles before I found the microbe in the blood.

It was not known before I made that experiment that dogs were subject to surra disease.

I brought the infected pup with me on my return to Army Headquarters at Simla, in order to study the progress of the disease in him, and to learn what I could by passing the disease on from him to other animals, to know whether the disease with the specific microbe in question is really communicable by the milk only from mother to sucking pup, and whether the microbe may be found in the milk. Moreover, I was very anxious to show the living active microbe to other medical men, particularly to Dr. Cunningham, the Surgeon-General in India, and to Dr. Timothy Lewis, the Special Assistant to the Sanitary Commissioner with the Government of India, who had distinguished himself by his discoveries of blood parasites, officially reported and published in his illustrated monograph, a copy of which I have given to the Welsh National Library—it has been for a long time exceedingly scarce in the market.

Dr. Lewis, after examining the microbe in the blood of the pup, declared it was morphologically like what he had discovered in the blood of the brown rats of drains, described by him in the *Journal of the Royal Microscopical Society*, January, 1879, with some slight difference. These are now known as *Trypanosoma lewisi*. He emphatically controverted my opinion that they were pathogenic. The rats were, in his opinion, healthy.

In my official report upon surra in horses and camels at Dera Ismael Khan, I stated 'During the progress of the disease the parasite does not remain always in the same proportion, *it comes and goes in successive broods*. The general symptoms are also variable. I have not been able to prove that a definite relation exists between the variable number of the parasites present and the course of the symptoms, but I think it is probable.' Relation was afterwards proved to exist by Steel's observations upon surra in Burma.

The following extracts from my records of cases in the appendix to my report may interest you:—

CASE 1. 'It is worthy of note in this case that the urine became slightly albuminous with the disappearance of the parasites from the blood. I found nothing abnormal in the deposit from the urine examined carefully for casts.'

CASE 2. 'Note that in this case albumen was found in the urine throughout, and it appeared to have no relation with the disappearance of the parasite from the blood, as Case 1 led me to suppose. The structure of the kidney—post mortem—was perfectly normal under the microscope, and I found no casts in the urine. The structure of the liver was also normal, though all the mucous membranes were tinged yellow. I examined these organs with great care in this case, as in Case 1, directly after death (the animals were killed purposely for my examination). The weather was exceedingly hot, and the temperature within a cool bungalow about 82° every day, but I had plenty of ice in large felted baskets to preserve the organs while I examined them. . . I examined the dung carefully morning and evening for worms, etc., and found nothing abnormal. With regard to the swelling of the sub-maxillary gland and discharge of nasal mucus, I found this in four cases only out of fifty.'

CASE 3. 'It should be particularly noted in this case, with regard to the life-history of the blood parasites, that they do not disappear from the blood entirely when it becomes difficult to find one in a drop of blood; but that when one brood or generation dies, there are ova or spores left for the development of another brood. Thus, in this case, on the 26th September the parasites were swarming in each drop of blood. On the 29th, only one parasite was found in two drops of blood examined; on the 7th October great numbers were found in a drop—there were more than I could

count on a slide. I was not able to see this case again from the 9th until the 16th, when no parasite could be found in a drop of blood examined.' (I had been away visiting other Posts on the frontier.)

CASE 5. 'This case has fully confirmed the experiments of Case 4 with regard to the disease being communicable by the subcutaneous injection of the blood containing the parasite, and it even more strikingly illustrates the short stage of incubation as compared with the first two experiments. The parasites were found swarming in the blood of this case, and the visible mucous membranes assuming the appearance peculiar to surra *four and a half days after the inoculation*. The next point of note is the shock the nervous system received a few hours after the inoculation, as shown by the intermittent pulse, the difficulty of feeling the pulse except at the heart by auscultation, and the lowering of the temperature. It is surprising how little the appetite of this case was affected afterwards, how rapidly the animal wasted while he ate as well as he did in health.'

'No local irritation followed when the hypodermic syringe punctured the skin in the operation of inoculation in any experiment.'

CASE 6. 'No parasite found in the blood of this mare five and a half days after she drank the surra blood, but two days later they were found swarming in each drop. The outward symptoms characteristic of surra appeared with the advent of the parasites. In this case, as in those inoculated under the skin, there was first a depression and then an abnormal elevation of temperature marking the transition period from health to disease.'

CASE 7. 'The mucous membranes first showed the peculiar yellow colour of the surra on the fifth morning after the surra blood was taken into the stomach, and the parasite was not found in the blood in this case until the seventh morning. This case fully confirms the experiment of Case 5, that the disease surra, with its peculiar blood parasite, may be communicated by drinking the blood of surra as well as by subcutaneous inoculation; also that it takes longer for the virus to pass into the circulation by drinking much of the blood than by injecting a little of it beneath the skin. The experiments prove that the common belief of the seeds of the disease lying dormant in the system for many weeks is entirely wrong.'

These extracts of the detailed reports I made of the cases show

you the drift of my observations. You will appreciate the strong wish I had to find the meaning of the leucocytosis in relation to the parasites of surra and of anthrax fever, and why the surra microbe came and went so regularly in course of the disease—in the dog as in horses and camels. Dr. Lewis had not observed it in rats affected with a similar microbe, nor had he read of any other microbe in the blood of any animal conducting itself in that manner. He did not think that, nor the leucocytosis, of any importance worth troubling about.

Both Dr. Cunningham and Dr. Lewis had in their official reports committed themselves positively to the opinion that *no microbe found in the living blood of any animal was pathogenic*. They did not doubt my reports of what I had observed in anthrax and surra, but they, as strongly as they could use words officially, negatived the conclusions I drew from my observations. We discussed the subject in private conversations, of course in the most friendly spirit.

While you read the following extract of my report for the information of His Honour the Governor of the Punjab, dated November, 1880, bear in mind it was some time before Koch published his classical postulates. I was groping in the dark with psychological rushlights only, impelled by a very strong scientific faith that the discovery of important pathological facts was imminent in the direction I was trying to go.

The question suggested by these facts is, whether the presence of the parasite is the cause of the disease, or whether the disease is the cause of the appearance of the parasites. That they are most intimately related to each other is, in my opinion, beyond reasonable dispute. There are some eminent pathologists in India who deny the parasite origin of specific blood diseases; they say the cause of all such diseases, from smallpox to anthrax fever, is not any organic spore, or germ, or parasite of any kind, but it is some purely chemical agent which has never been discovered, and these organisms develop at once in blood which has been so chemically altered, each chemical virus developing its specific organism; the spores, or ova, of which are *supposed* to be in normal blood, ready to develop as soon as chemistry favours them. The organisms themselves, when developed, are supposed, by these authorities, to be harmless.

‘That is one of the most vexed questions of the present day in the pathological world, and it strikes hard at the root of the

science and practice of sanitation.' Against the above theory, it is contended :—

Firstly : 'That we should judge the unknown by the known. This supposed specific disease virus is not known to chemistry, and there is no known pure chemical agent that acts in any way analogous to the specific virus of fevers, one dose of which, when taken into the stomach, gets into the circulating blood, multiplies itself there a million fold, and produces a constitutional disturbance lasting for weeks or months—as in surra ; and a few drops of that living blood, after the lapse of many weeks since it was first chemically impregnated, if placed under the skin of a healthy animal will, by chemistry alone, multiply and reproduce the same disease again, and so on *ad infinitum*. In considering this subject, we must bear in mind that the same blood does not remain long circulating in the body, but that it is in a constant state of renewal, and, so far as we have any knowledge of pure chemical non-corrosive poisons, when only one moderate dose is given, it either precipitates and remains harmless, because there is too little of it, or else it is decomposed and passed out with the effete blood, and leaves the system uninjured, or else it rapidly causes death. A small dose of pure chemical poison has never been known to multiply itself in the system, nor has there been anything analagous to that performed by any ingeniously contrived apparatus at any chemical laboratory that I am aware of.'

Secondly : 'It is contended that specific self-propagation, like by like, is the most characteristic feature of living organisms, as distinguished from non-vital chemical agents : so that if we never found any foreign living organisms in the blood of specific disease, reason by analogy from known to unknown would lead us to believe that the disease was due to propagating living organisms present in the blood, though unseen.'

Thirdly : 'It is contended that the microscope has enabled us to see such living organisms as an efficient cause, in the blood, to develop the diseases in question. In reply to this, they say that organisms, so like as not to be clearly distinguished by the microscope, are found also in some healthy subjects, and appear to do no harm. Therefore, we should not conclude that the one is any more virulent than the other. The answer to that objection is this, we must not always judge by appearance, but rather by

actions. There is an old saying, worthy of being remembered, in our intercourse with men that "A fool is considered wise until he speaks." It is not by vision, but by noticing results, that we usually first learn to distinguish the poisonous snake from another, not very unlike it, which is harmless, and a berry is deadly poisonous, while another, very like it, is wholesome. After we learn that difference in effect, we notice specific differences in appearance, but if these snakes and berries were so small as some of the organisms we find in the blood, no microscope could enable us to see the slightest differences between the poisonous and non-poisonous. We must, therefore, judge them by their results or associations, and we do it in this manner. We often find organisms A, B and C in the blood of healthy animals, and therefore conclude that they are harmless, but we also find organisms indistinguishable in shape from A, B and C present in the first stage and throughout the course of diseases 1, 2 and 3; A always abundant in 1, never in 2 or 3; B always abundant in 2, never in 1 nor in 3; C always abundant in 3, never in 1 nor in 2. The blood of 1, 2 and 3 contain the organisms A, B and C respectively, if put into the stomach or under the skin of healthy animals will invariably reproduce 1 + A, 2 + B, and 3 + C, but not other associations. Again, if we destroy A, B, C, or remove them from the blood of 1, 2, 3, by filtration, and then inoculate healthy animals with the blood so treated, we shall either reproduce the diseases in a very mild form or not at all. A pure chemical virus would be in a state of solution, and would not be affected by the filter, from which results we conclude that the organisms A, B and C are the causes of the diseases 1, 2 and 3, though from other observations we find that organisms indistinguishable from A, B and C in *appearance* are harmless.'

'The parasitic organisms A, B and C may cause disease by secreting chemical virus, or by causing some kind of fermentation in the blood.'

That suffices to give you some idea of the professional controversy I was engaged in at the early dawn of the present day of pathogenesis. Remember how impossible it is to differentiate positively some bacteria in their living state, which are easily differentiated when they are dead and stained. We had no stain for them in India at the time of my report. I may be allowed to state now, after much experience in staining, that we formerly, by close,



continued observation of living bacteria, especially the bacilli, noticed differences that few modern bacteriologists are aware of—time is valuable, there is too much haste to fix the bacteria on the glass by passing it through the flame, which alters their shape. Moreover, the pathological changes in the blood corpuscles, in the development of small plates, are too often not observed so closely as in pre-staining days, because of the time necessary to do so.

The Surgeon-General and the Chief Sanitary Officer, and all the senior Medical Officers in India at that time, continued to maintain their opposition to the theory of pathogenesis advocated by me: they officially sat upon me heavily, but the Government printed and circulated my reports, and I have been gratified by the assurance of some younger men that my statements spurred them to follow with much success the line I had indicated for further investigation.

I copy the following extract from my report upon camels I found affected with surra at Dera Ismael Khan:—

‘On examining the mucous membranes I found the first four on the list presented the characteristic appearance of surra in horses—yellow with petechiae—but No. 8/79 had petechiae without the yellowness; he was blanched, his eyes were dry, the others wept. Neither of them had dropsical swellings, nor had they any previously, I was told. On examining the blood by the microscope I found the parasite of surra in countless numbers, and very active in the first four, but not one in No. 8/79. I examined many drops of his blood, and failed to find one. He had in his blood what I did not find in the others, the embryos of a filaria which appeared to me to answer exactly the description given by Dr. Timothy Lewis in his monograph on the *Filaria sanguinis hominis*. About ten or twelve were present in every small droplet of blood. I have submitted specimens to Dr. Lewis, but he has not yet had time to determine whether they are exactly the same as those found in man or not; he is inclined to think they are different. The urine of each of these camels was normal.’

Camel No. 8/79 was killed by the usual Moslem method of throat-cutting, for me to make a post-mortem examination, which I reported as follows:—

‘There was no abnormal amount of serum in the peritoneal cavity, nor fluff of lymph such as I found in surra horses. The organs were all healthy. But in the right ventricle of the heart, and

in the pulmonary arteries, I found tangled masses of adult filaria several inches long, which I supposed to be the mature form of the embryos which I had found by the microscope in the living animal. I have not had time to examine them in detail, neither has Dr. Lewis, to whom I have given specimens, but they are certainly thicker than the single specimen of *Filaria sanguinis hominis* which he found in man.'

Dr. Lewis read a paper upon those I found, giving full detailed description, showing how they differed from any found previously, and named them *Filaria evansi* (*vide Proceedings, Asiatic Society of Bengal, March, 1882*).

Before I was able to complete my official report of my work at Dera Ismael Khan, I received orders to proceed as soon as I could to a very different climate, from extremely dry to extremely moist, to investigate and report upon a fatal disease in ponies on the tea estates of Kachar, and other parts of Assam, which I found to be anthracoid bacilli in the blood, with leucocytosis, etc.

On my return to Calcutta, I found Dr. Lewis had come then with the Government of India—from Simla—and had brought the surra puppy in a wretchedly wasted condition. The parasite swarmed actively in the blood. I was disappointed that Dr. Lewis had not made any further observation upon them, nor made any experiment by transference. He was positive, as he was at Simla, that the parasite was not more pathogenic in the dog than those he found like them in the rats were. He believed the pup suffered only from the common 'distemper' of dogs. I asked him how he knew the rats were healthy: he had not taken their temperature, nor kept them long under observation. A casual observer would not think the pup was not healthy when I gave it to him; he did not think the pup was ill then, but I knew he was because of my closer observation and better knowledge of dogs. Probably an expert in rat pathology would say the rats in question were not healthy. It was useless talking. He and Surgeon-General Cunningham remained obdurate; they seemed to regard me as one with 'a bee in his bonnet.' As I said in the foregoing, I was particularly wishful to utilise the pup to inoculate another bitch, to prove under more careful conditions whether the surra parasite did pass via the lactial glands to sucking pups—that question appeared to me of great scientific importance, whether the microbe was pathogenic or not. I was then transferred

from Bengal to be Inspecting Veterinary Surgeon of the Madras Presidency, an appointment for five years, stationed at the Army Headquarters, and ordered to go forthwith. I did not take the pup with me, because I could not keep him sufficiently isolated not to spread the infection—the disease had now been reported in the Madras Presidency—so Lewis destroyed him with poison.

I returned to England, December, 1885, and was stationed at Woolwich as Inspecting Veterinary Surgeon of the district (Army), and, as soon as I could, arranged to study bacteriology in all its practical technicalities at Crookshank's laboratory, King's College, London\*—it was delightful work. I expressed to him my wish to experiment in transferring *Trypanosoma lewisi* (*Trichomonas lewisi* he called it) from rat to monkey, to find whether it would become diseased in consequence, and if so, how affected—would the microbe of the rat live and multiply in the monkey? If so, it would probably do likewise in man. The subject was submitted to Lister, to the Presidents of the R.C.P. and the R.C.S., and others, who agreed.†

I retired from the Army in 1890, and settled down here for the convenience of my children's education at school and college. During the University College, North Wales, Session 1890-1, the Council requested me to deliver a course of lectures upon Veterinary Hygiene in the Agricultural Department. I consented, and was re-appointed annually for over twenty years. I resigned on account of my health.

All my medical studies have been *con amore* only, my ample reward being in the scientific attainment. I never applied for any appointment excepting to the Army. I did not try to qualify for medical registration in England. I became a member of the British Medical Association in 1870 on my return from Canada, or in 1871, I forget which.

Now I must conclude, having written much more than I intended in commencing this letter. [I cannot write so fast now as I used to, having cataract in both eyes, so this has been running, or rather walking, for many days.] However, it may not be unfitting if I add to the story of my medical course (what you ask of me) a few lines showing my collateral studies.

I had read the *Vestiges of Creation* before Darwin published his

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\* I also attended a course of lectures at the Royal Sanitary Institution, and studied practical sanitation there.

† The experiment was not carried out.—EDD.

*Origin of Species*, which captivated me. Spencer's *First Principles*, published two or three years later, made me sit at his feet ever after. Next came Lyell's *Geological Evidence of the Antiquity of Man*, plus his *Principles of Geology, or the Modern Changes of the Earth and its Inhabitants*—enlarged edition of 1876, and Tylor's *Primitive Culture*, plus Frazer's *Golden Bough*. In biology I was particularly interested in heredity, and the subject of the continuity of Germ Plasm and psychology was the principal object of my thoughts for a long while, reading all the leading investigations I could find published in English to help me.

All such spiritual pabulum I devoured in a hungry state of mind, so I was lifted and carried on the crest of the greatest scientific wave in history. Moreover, I was aged 13, the dawn of manhood, in the great revolutionary year 1848 that shook Europe. The conversations of my father then fixed me in rationalism and democracy. I followed Cobden and John Bright closely. I am sure there would have been no trouble in Ireland *re* Home Rule, etc., if Parliament had settled the land question as Mr. Bright recommended persistently. My father was the first in Western Wales to sign the teetotal pledge, and he formed the first Teetotal Society at Towyn in 1837, and kept his pledge so long as he lived. I was then aged 2, and I have remained teetotal. I have signed the pledge many times, because I found at many meetings in different parts of the world it was a great help if somebody went forward to sign directly after the chief speech was delivered. For some time after I entered the Army I was the only teetotaler in the officers' mess. When I retired from the Army teetotalers were common. My recollection of the changes in the medical use of alcohol is surprising. The subject of the changes in the fashion of medical treatment is interesting; it is curious how many medical men follow the herd, like sheep. The 'psychology of the crowd,'—I must stop at that. If I have bothered you with too much, pardon me.

Yours truly,

GRIFF. EVANS.

25 October, 1916.

# OBSERVATIONS ON THE CYSTS OF THE COMMON INTESTINAL PROTOZOA OF MAN

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## INTRODUCTION

The following remarks are presented mainly by way of an explanation of the accompanying plate which has been prepared for this journal at the request of the Editors. Considering the large amount of descriptive work already published on the human intestinal protozoa, it is not to be anticipated that much that is new will here be added to our knowledge of the morphology of the cysts of these organisms. Yet it was considered desirable that the present opportunity, when so much material is available, should not be allowed to pass without making some drawings of the cysts commonly found during the routine examination of the stools of convalescent dysenterics. It is recognised that these cysts have been figured many times by many different authors, but the figures have generally been drawn from fixed and stained preparations, and while some are excellent it must be admitted that others are less so. On the other hand, figures have appeared which are obviously diagrammatic. The need was felt for a series of drawings depicting the common human protozoal cysts as they may be seen by the student of Tropical Medicine or by anyone engaged on routine work for the purpose of diagnosis. With this object in view the present figures have been prepared. To one who has had considerable experience, it is often sufficient to examine the cyst-containing material in saline, but if the material be mounted in iodine solution,\* the cysts become stained, and the nuclei, which were perhaps invisible or difficult to see, will be found, as a rule, to stand out more clearly defined. The majority

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\* Weigert's solution = iodine 1, potassium iodide 2, distilled water 100.

of the figures which appear on the plate were made from cysts stained in this way. While it is admitted that exact cytological detail cannot be obtained by this method, it is nevertheless true that the essential features of most cysts can be ascertained, and it is the method generally adopted in practice when a diagnosis has to be made. It is worth bearing in mind, however, that no matter how well defined a cyst may appear in iodine, it is not easy to represent the appearance in a black and white drawing, which lacks the coloration which the iodine gives—a feature, in my opinion, of considerable importance.

Notes on the appearance of cysts stained with iodine will be given under each protozoon described.

#### **ENTAMOEBA HISTOLYTICA**

One of the most important of recent discoveries regarding this organism is the fact that there is great variation in the size of its cysts. It is now known that infections occasionally occur in which the cysts are well over 15 microns in diameter, and it is definitely established that in a large number of infections the cysts are well below 10 microns. Thus, instead of stating that *E. histolytica* produces cysts varying from  $10\mu$  to  $15\mu$  in diameter, it is now more correct to state that the size ranges from  $5\mu$  to  $20\mu$ . It is not to be supposed, however, that cysts having this wide range in size will be found in every infected case. Such an occurrence is exceptional. An analysis of the results obtained in this laboratory during the past year shows that of the total number of *E. histolytica* infections detected about 35 per cent. consisted of cysts varying from  $6\mu$  to  $9\mu$ , while in the remaining infections, the great majority of the cysts varied from  $10\mu$  to  $15\mu$  in diameter. A few individual cysts about  $18\mu$  have been observed, and a few cases were found where the infection obviously consisted of both large and small cysts, and all gradations in size from  $6\mu$  to  $15\mu$  were observed. The small cysts have been noted by various workers, and in an important paper Wenyon and O'Connor (1917) have given a careful study of them, and have come to the conclusion that they belong to a distinct race or strain of the species *E. histolytica*. This view is also held by Dobell and Jepps who, in a recent and valuable paper (1918), have

demonstrated the existence of several races within the species, distinguishable from one another by the size of the cysts which they produce. In the accompanying plate small cysts of *E. histolytica* are shown in figs. 1-4, and these should be compared with figs. 5-9, which depict larger cysts of the same species.

The importance of the foregoing remarks on the size of *E. histolytica* cysts is at once obvious, when it is remembered that in human faeces other cysts occur, of similar sizes and of somewhat similar appearance, with which the cysts of *E. histolytica* may possibly be confused. On the one hand, the cysts of *E. nana* which are  $7\mu$  or  $8\mu$  in diameter may be mistaken for the small cysts of *E. histolytica*, and on the other, small cysts of *E. coli* at certain stages in their development may be confused with the larger cysts of *E. histolytica*. We are thus compelled to abandon size of cyst as a certain criterion for diagnostic purposes. Of greater importance, as has been often pointed out, and again emphasised by Dobell and Jepps (1917), is the structure and number of the nuclei. The fully developed cyst of *E. coli* has eight while the fully developed cyst of *E. histolytica* has four nuclei. We shall deal with this tetranucleate stage first. If it is a small cyst of  $7\mu$  or  $8\mu$  in diameter it can be distinguished from a tetranucleate cyst of *E. nana* by the structure of its nuclei (compare figs. 4 and 10). Further, the nuclei of an *E. histolytica* cyst are nearly always clearly defined in iodine solution, while in the vast majority of *E. nana* cysts it is extremely difficult to distinguish the nuclei clearly (figs. 12 and 13). If the cyst is large, and comes within the range of the size of *E. coli* cysts, we are almost entirely dependent on the structure of the nuclei for a correct diagnosis (compare figs. 8 and 14). Even if the two cysts depicted in these figures had been of the same size, the nuclear structure would still provide a differential character. In my experience, however, the tetranucleate stage of *E. coli* is not commonly found, though this, of course, does not dispose of the difficulty. The appearance of the cytoplasm is often of considerable help, for it generally stains less uniformly in *E. histolytica* than in *E. coli* cysts. If chromatoid bodies (chromidial bars) are present, their shape is of some value. In *E. histolytica* they are commonly square or round-ended rods, while sharp-pointed, ragged-ended, or large irregular blocks are more characteristic of *E. coli*.

We may now briefly refer to *E. histolytica* and *E. coli* cysts containing fewer than four nuclei. The uninucleate and binucleate stages of *E. histolytica* are quite common. They are less common in *E. coli*. There should, however, be little difficulty in distinguishing the two species in these stages of development. The difference in the structure of the nuclei is well known (see figs. 5, 6, 7, 15 and 16). In these stages, also, vacuoles which contain glycogen are common in both species, and the appearance of these in iodine is important. In *E. histolytica* the vacuole is generally ill-defined and not very deeply stained (figs. 1, 5 and 6). In binucleate cysts of *E. coli* the vacuole is commonly large, occupying nearly the whole cyst, and is always deeply stained with well defined edges (fig. 15). In some binucleate *E. coli* cysts, however, the vacuole appears crescent-shaped, round one side of the cyst. Not uncommonly *E. histolytica* cysts possess numerous vacuoles (a type which is frequently encountered in relapses after treatment) and these do not always stain in iodine (fig. 7). On the other hand, uninucleate and binucleate cysts of both species occur not infrequently without vacuoles, in which case the nuclear structure remains as a differential diagnostic character.

#### **ENTAMOEBA COLI**

The difficulties that are likely to be encountered in distinguishing this species in certain stages of encystment have already been noted. The fully developed cyst containing eight nuclei is the stage most commonly found, and cannot possibly be mistaken if the nuclei are carefully counted, even when its dimensions are within the range of size of *E. histolytica* cysts (see fig. 17 and compare with fig. 8). *E. coli* cysts show great variation in size, spherical cysts ranging from about  $12\mu$  to over  $30\mu$  in diameter. Dobell and Jepps have measured *E. coli* cysts as small as  $11\mu$ , and Wenyon and O'Connor have recorded  $38\mu$  by  $34\mu$  as maximum values. These larger cysts contain as a rule sixteen nuclei. Chromatoid bodies are not uncommon in *E. coli* cysts, and the old distinction of their presence in *E. histolytica* and their absence in *E. coli* cannot be any longer maintained. As already noted, these bodies, which are best studied in cysts mounted in saline, are as a rule less regular in shape in



*E. coli* than in *E. histolytica* (compare figs. 2, 9 and 18). A fairly common appearance of the eight-nucleate *E. coli* cyst is shown in fig. 19. There is a central mass of granular cytoplasm, in which several or all of the nuclei are embedded, surrounded by more alveolar and less deeply staining cytoplasm. The nuclei are often more or less disintegrated or distorted in appearance, and the condition is probably abnormal, although James (1914) regards the phenomenon as a normal stage in encystment.

In a paper on the measurements of cysts which appears in this number of the *Annals of Tropical Medicine and Parasitology*, Smith (1918) has dealt fully with the differences between the cysts of *E. histolytica* and *E. coli*, and has drawn up a diagnostic table giving the main points of distinction. It may be useful to give a similar tabular statement in the present paper, but it should be borne in mind that while the distinctions apply generally, some of them may break down in individual instances.

<i>E. histolytica</i> cysts.	<i>E. coli</i> cysts.
Size, $5\mu$ to $20\mu$ in diameter, most commonly $6\mu$ to $15\mu$ .	Size, $11\mu$ to $35\mu$ in diameter, most commonly $14\mu$ to $22\mu$ .
Nuclei 1 to 4 in number.	Nuclei 1 to 8, occasionally 16.
Peripheral chromatin of nucleus of small granules more or less evenly distributed.	Peripheral chromatin of nucleus of larger unevenly distributed blocks.
Cytoplasm greenish in fresh condition, typically not uniform in appearance.	Cytoplasm greyish in fresh condition, more uniform in appearance.
Vacuoles one or more, usually faintly stained by iodine with ill-defined edges.	Vacuole generally single, usually deeply stained by iodine with sharply defined edges.
Chromatoid bodies more frequent, rod-shaped with square or rounded ends.	Chromatoid bodies less frequent, irregular in shape with pointed or splintered ends.

### ENTAMOEBIA NANA

This entamoeba, named by Wenyon and O'Connor (1917), has been fully described by these authors and by Dobell and Jepps (1917). Its cysts are frequently encountered in the examination of both dysenteric and normal stools, and as already mentioned, it is important to distinguish them from the small cysts of *E. histolytica*. They are oval or roundish structures about  $8\mu$  to  $10\mu$  long, or  $7\mu$  or  $8\mu$  in diameter. They contain numerous highly refringent

granules, and if they are allowed to stain in iodine for some time (fifteen minutes or longer) it is often possible, in some of the cysts at least, to make out the nuclei, which vary in number from one to four according to the stage of development. The tetranucleate cyst shown in fig. 10 was uncommonly well defined, and figs. 12 and 13 depict what is more generally seen. The exact structure of the nucleus, with its large, usually eccentric karyosome, can only be obtained by staining with iron haematoxylin or some other suitable stain. A feature of *E. nana* cysts which is common in the binucleate stage, though not so frequent in the tetranucleate, is the presence of a large glycogen-containing vacuole which stains dark brown in iodine (fig. 11). It is, moreover, clearly defined, and this fact should be of service in distinguishing these cysts from the small cysts of *E. histolytica*, in which the vacuole is less deeply stained and not so sharply defined.

#### ***CHILOMASTIX (TETRAMITUS) MESNILI***

The cysts of this flagellate may possibly be confused with those of *Entamoeba nana* (compare figs. 11 and 23). They are about the same size, but the characteristic protuberance at one end of a Tetramitus cyst, giving it a lemon-shaped appearance, is a feature which should help in the determination of the great majority of the cysts of the flagellate. Oval and spherical cysts have been described by Dobell and Jepps, but they do not appear to be common. The nuclear structure is again one of the most important characters, and its essential features can readily be observed in cysts that have been allowed to stain in iodine for ten minutes or longer. The nucleus is large, and possesses at one pole a distinct mass of chromatin giving the appearance of a signet ring (fig. 22). In addition, staining with iodine brings out quite clearly the outline of the remains of the cytostome of the flagellate, and this feature should simplify the identification of the cyst. Occasionally the cysts of *T. mesnili* contain a large, well defined mass of glycogen which stains dark brown in iodine (fig. 23). It often renders the cytostome invisible, and when this is the case care should be taken not to confuse the cyst with that of *E. nana* or with small forms of iodine cysts, which will be referred to below.

**GIARDIA (LAMBLIA) INTESTINALIS**

The cysts of this flagellate are among the most easily recognised of all the protozoal cysts occurring in human faeces. They are nearly always oval-shaped structures, though occasionally almost spherical forms have been observed, and these may bear a fairly close resemblance to cysts of *E. histolytica*. Mounted in iodine the internal structure of the cyst can readily be distinguished. Most commonly four nuclei are present, generally lying towards one end of the cyst, and remains of the intracytoplasmic structure of the flagellate are extremely characteristic (fig. 20). Staining with iodine brings out a striking difference between two kinds of *Lambli*a cysts which has not hitherto been noted. In almost every infection, if examined sufficiently carefully, it will be found that some of the cysts stain brown while others are stained a bluish-grey or slate colour. Observations show that in conjunction with the different staining reaction there is a distinct difference in the size of the two kinds of cysts. The brown ones are larger, the majority varying from  $12\mu$  to  $15\mu$  in length, while the blue staining cysts are smaller, the average length being  $10\mu$  or  $11\mu$  (figs. 20 and 21). As already mentioned, the differentiation between these two forms of cyst is most marked when they are examined in iodine, because of their different colour, but they can also be distinguished in saline partly by the difference in size and partly by the more granular and somewhat degenerate appearance of the smaller and bluish-staining type. What these differences signify is not yet determined.

**IODINE CYSTS**

These cysts were first noted by Wenyon (1915), and have been more fully described by Wenyon and O'Connor (1917). They vary greatly in size, covering practically the same range in size as the cysts of *E. histolytica*, and it is with these that they are most likely to be confused. This is particularly the case when the structures are examined in saline. The iodophilic body which is most characteristic of Iodine Cysts may simulate the chromatoid body of an *E. histolytica* cyst, though it is generally not rod-shaped but rounded or lobed. In iodine this inclusion stains deep brown and

has well-defined edges. Occasionally, Iodine Cysts are found without the iodophilic body, and it is then that the organism may very closely resemble a cyst of *E. histolytica*. The nucleus is, however, distinctly smaller than the nucleus of a uninucleate *E. histolytica* cyst, and is quite different in structure (see fig. 24 and compare with figs. 1, 2, and 5). (Fig. 24 was drawn from fixed material stained with iron haematoxylin. The iodophilic body shows as a clear space, but in a cyst mounted in iodine this space would appear dark brown in colour and the nuclear structure would be less clearly defined). It should be noted also that small Iodine Cysts may be confused with *E. nana* or Tetramitus cysts when these contain, as they sometimes do, deeply staining glycogen vacuoles. Iodine Cysts are not protozoal. They probably represent some stage in the life-history of a vegetable organism but so far all attempts to cultivate them have failed.

#### **BLASTOCYSTIS HOMINIS**

This organism, like that described under the name of Iodine Cyst, is also of a vegetable nature. It is exceedingly common in human faeces, and may possibly be mistaken for some of the protozoal cysts already dealt with, and in particular, it may be confused with encysted stages of *E. histolytica*. Blastocystis varies in size from  $5\mu$  to over  $20\mu$  in diameter. A large number of infections consist only of small forms, about 7 or 8 microns, and these may occasionally be troublesome to distinguish from small cysts of *E. histolytica*. Blastocystis, possesses, however, a much thinner enveloping membrane, within which there is a narrow rim of cytoplasm, nearly always most conspicuously developed at opposite poles of the structure. The centre of the organism is occupied by a reserve body, but in many instances this body has disappeared and the structure then apparently possesses a central vacuole (fig. 25). In the cytoplasm a varying number of nuclei occur. Considerable variety of form is met with in Blastocystis. Dumb-bell shaped individuals are not infrequently encountered, representing a stage in the transverse division of the organism, and multiple reproductive cysts, which are considerably larger in size than single forms, have been described by Alexeieff and Wenyon and O'Connor.

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## EXPLANATION OF PLATE

All the figures (except 9 and 24) were drawn, from cysts stained with iodine, with the aid of a camera lucida at a magnification of 3,300. They have been reduced in reproduction.

Figs. 1-9. Cysts of *Entamoeba histolytica*.

- Fig. 1. Uninucleate cyst containing vacuole. Diameter  $8\mu$
- Fig. 2. Uninucleate cyst with a single chromatoid body. Diameter  $8\mu$
- Fig. 3. Binucleate cyst. Diameter  $7.5\mu$
- Fig. 4. Tetranucleate cyst. Diameter  $8\mu$
- Fig. 5. Uninucleate cyst with diffuse staining vacuole, size  $13.5\mu \times 12\mu$
- Fig. 6. Binucleate cyst with diffuse staining vacuole. Diameter  $12\mu$
- Fig. 7. Binucleate cyst with several vacuoles unstained by iodine. Diameter  $10\mu$
- Fig. 8. Tetranucleate cyst. Diameter  $12.5\mu$
- Fig. 9. Binucleate cyst with typical chromatoid body. Diameter  $11\mu$ .  
Cyst as seen in saline.

Figs. 10-13. Cysts of *Entamoeba nana*.

- Fig. 10. Tetranucleate cyst, nuclei remarkably clear. Size  $9\mu \times 8\mu$
  - Fig. 11. Binucleate cyst with deeply stained mass of glycogen. Size  $9\mu \times 7.5\mu$
  - Fig. 12. Binucleate cyst, nuclei faintly stained. Size  $8.5\mu \times 7\mu$
  - Fig. 13. Uninucleate cyst, nucleus faintly stained. Size  $8.5\mu \times 7\mu$
- In all four cysts the refringent granules of volutin were clearly discernible.

Figs. 14-19. Cysts of *Entamoeba coli*.

- Fig. 14. Tetranucleate cyst. Diameter  $17.5\mu$
- Fig. 15. Binucleate cyst with large deeply stained centrally placed vacuole. Diameter  $16\mu$
- Fig. 16. Binucleate cyst without vacuole. Diameter  $18.5\mu$
- Fig. 17. Eight nucleate cyst. Diameter  $13\mu$
- Fig. 18. Eight nucleate cyst with pointed chromatoid bodies. Diameter  $16\mu$
- Fig. 19. Probably abnormal eight nucleate cyst. Diameter  $17\mu$

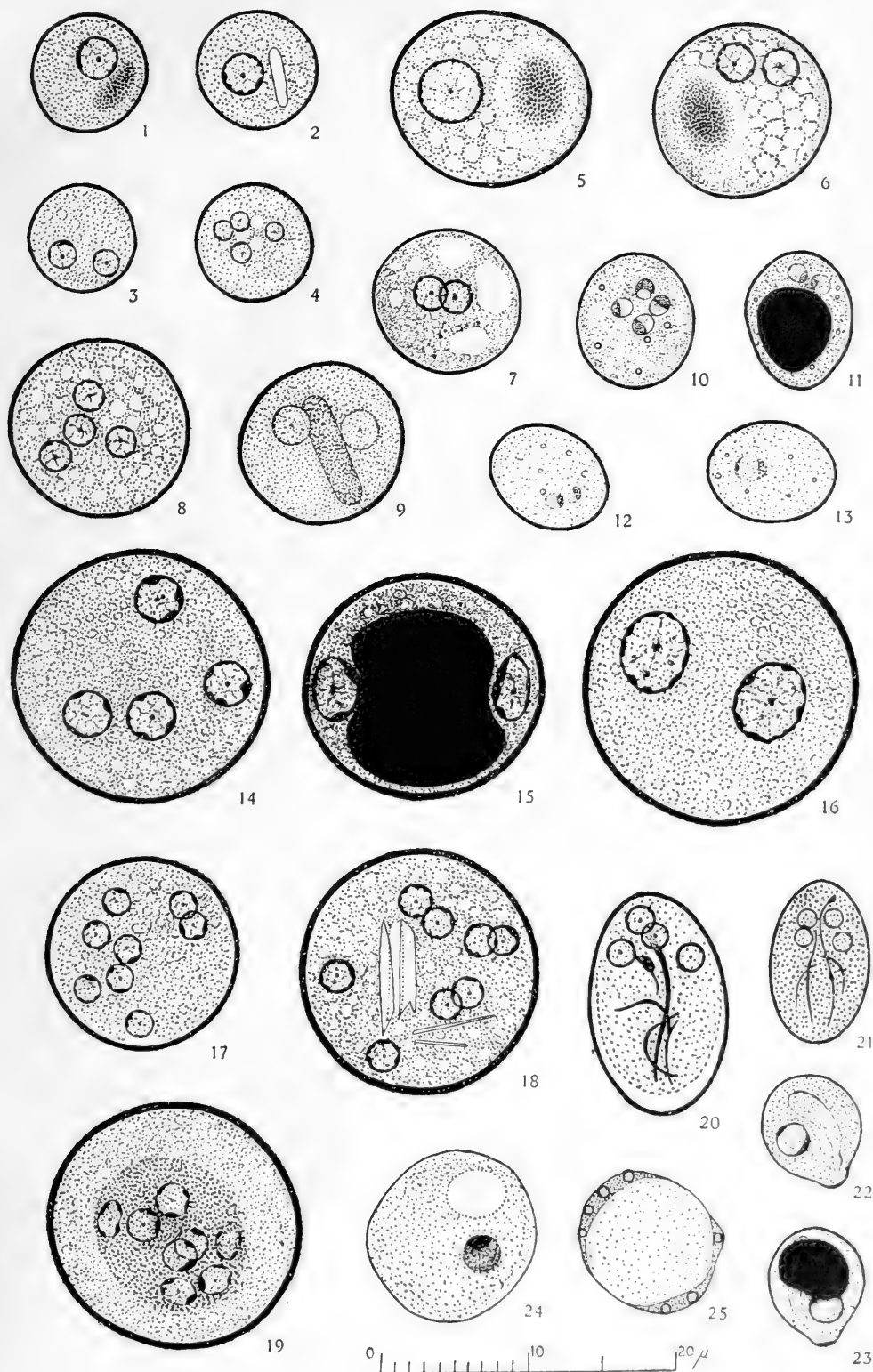
Figs. 20-21. Cysts of *Giardia intestinalis*.

- Fig. 20. Large brown staining cyst. Size  $15\mu \times 9.5\mu$
- Fig. 21. Small bluish-grey staining cyst. Size  $10\mu \times 6.5\mu$

Figs. 22-23. Cysts of *Chilomastix mesnili*.

- Fig. 22. The cytostome and nucleus clearly visible. Size  $8.5\mu \times 7.5\mu$
- Fig. 23. The cytostome and nucleus partially obscured by large deeply staining mass of glycogen. Size  $8.5\mu \times 7.5\mu$
- Fig. 24. Iodine cyst drawn from specimen stained with iron haematoxylin. The clear space would appear dark brown in colour if stained with iodine and the nucleus would be less sharply defined. Diameter  $11.5\mu$

- Fig. 25. *Blastocystis hominis*. Diameter  $10\mu$







# MEASUREMENTS OF AND OBSERVATIONS UPON THE CYSTS OF *ENTAMOEBA HISTOLYTICA* AND OF *ENTAMOEBA COLI*

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From April 22nd, 1917, until March 4th, 1918, the writer measured the dimensions of 2,833 cysts of two of the intestinal entamoebae of man, *E. histolytica* and *E. coli*. The results of these measurements are given in the present paper. At the time each measurement was made the nuclei of the cyst were counted and their number recorded. A note was also made of the presence or absence of chromatoid bodies and vacuoles. The main results of these observations are recorded here also.

## METHODS

The majority of the stools from which the cysts to be measured were taken were those of convalescent dysenterics, and were sent to the laboratory for the usual routine examination for dysentery. Cysts were also measured from a small number of carriers of *E. histolytica* who had not had dysentery. Stools in which cysts had been found by the routine examination were taken at random and set aside for measurement. Fifty-nine per cent. of the cysts were measured on the same day as they were sent in, twenty-two per cent. on the following day, eleven per cent. two days afterwards, and the remainder later. With very few exceptions the cysts were measured in *iodine* (Weigert's solution), in order that their nuclei could be readily counted. A very small number of the cysts was measured in normal saline. The number of individuals whose stools

were used for cyst measurement was eighty. In thirty-four of these cases the cysts of *E. histolytica* alone were measured; in thirty cases only *E. coli* cysts were measured. In sixteen cases a double infection with *E. histolytica* and *E. coli* was present, and cysts of both were measured. Thus, in all, the cysts of ninety-six infections were measured. In one or two cases, though infections of both *E. histolytica* and *E. coli* were present, only cysts of one species were measured.

All the cysts of *E. histolytica* and the large majority of the cysts of *E. coli* were measured under the 1/12in. objective and No. 2 eyepiece. A comparatively small number of *E. coli* cysts was measured with the 1/6in. objective and No. 2 eyepiece. Each division of the scale of the ocular micrometer measured  $1.7\mu$  when the 1/12in. objective was used, and  $3.7\mu$  with the 1/6in. objective. It was considered possible to estimate by the eye one-tenth of the micrometer division, i.e.,  $0.17\mu$ , and values were actually recorded in this way, e.g., 7.1 divisions, 11.6 divisions. It is not claimed that the measurement thus obtained is accurate to the last figure. After considerable experience, however, it is estimated that measurements can be taken correct to the nearest  $0.5\mu$ , i.e., to about one-third of a scale division. This means that a cyst recorded as measuring 10.5 scale divisions may equally well be 10.6 or 10.4 divisions, but most probably is not 10.7 or 10.3 divisions. In the later part of the work 245 cysts of *E. histolytica* were measured with a scale whose divisions were exactly half of the width of the previous scale, i.e., the value of each division with the 1/12in. objective was  $0.85\mu$ , and with this scale the measurements were recorded to one-half a division, roughly  $0.5\mu$ , i.e., a similar accuracy to that claimed for the first scale.

In order to make sure that the figures of the curves given later should be significant, the figures recorded to one-tenth of a scale-division were added in groups of one-half a scale-division. Thus each group corresponds to a range of  $0.85\mu$ , and there is no question that accuracy of a higher order than this can be attained in the actual measurement.

As a general rule all the cysts encountered were measured in the order in which they were met. No omissions were made, so that a completely random selection of the cysts was ensured. The

insignificant departures from this rule were noted, so that their effect could be allowed for, if necessary, in making any deductions from the results obtained.

The species to which each cyst belonged was noted at the time of its measurement and a list of the criteria employed in diagnosis is here given, as the matter is a difficult and even controversial one. The difficulty was increased in this particular work by the following consideration. It was one of the objects of this work to establish a curve of the dimensions of the cysts for each of the species. It was therefore obviously inadmissible to use the size of the cyst as a basis of diagnosis. If, for example, all cysts below  $14\mu$  had been labelled *E. histolytica*, and all above  $14\mu$  *E. coli*, then the resulting curve of the dimensions of the species would have been valueless, as it would have been predetermined. It has been considered that a diagnosis could be reached on other points apart from size, and the points relied on are as follows:

#### 1. *The number of nuclei in the cyst*

All cysts with more than four nuclei were diagnosed as *E. coli*. Cysts with one to four nuclei may belong to either *E. histolytica* or *E. coli* as far as the number of their nuclei is concerned. As, however, four is the characteristic number of nuclei of the mature cyst of *E. histolytica*, it is present much oftener in *E. histolytica* cysts than in *E. coli* cysts. If, therefore, an infection had tetra-nucleate cysts prevalent in it, this was taken as an indication that *E. histolytica* cysts were present. In the case of individual cysts, however, the diagnosis could not be made on this point.

#### 2. *The character of the nuclei*

The nucleus of the cyst of *E. histolytica* has typically a smaller quantity of chromatin than has that of *E. coli*. The peripheral ring of chromatin is usually composed of small evenly distributed granules, while in *E. coli* the granules are larger and may even be irregular masses distributed irregularly round the nuclear ring. The general consequence is a greater visibility in the case of the nucleus of the *E. coli* cyst. The typical distinction is best seen in the mononucleate and binucleate cysts, and in these considerable reliance can be placed upon this character in the diagnosis. Even in the

tetranucleate cyst the greater visibility of the nuclei in *E. coli* is pretty obvious, though the differences in the structure of the peripheral chromatin ring between the one species and the other are perhaps not so marked in this stage.

A noteworthy effect of keeping stools containing *E. histolytica* cysts for a time is that changes occur in the nuclei of the cysts which tend to obliterate the distinction just pointed out between the cysts of the two species. The peripheral chromatin of the nuclei loses its typical fine granulations and seems to collect into larger, less regular masses. Even in fresh stools, cysts of *E. histolytica*, possibly somewhat degenerate, are encountered in which the peripheral chromatin of the nucleus seems more abundant than the normal, thus approaching to the kind of nucleus typical of the cyst of *E. coli*. This feature cannot therefore be relied upon alone in every case to distinguish the species. It is, however, most useful as a general diagnostic character.

### 3. *The character of the cytoplasm*

In *E. histolytica* cysts the cytoplasm as a whole is typically distinct from that of *E. coli*. Its colour seen fresh in normal saline is greenish-grey in *E. histolytica*, while in the cyst of *E. coli* it is paler. Though this is rather a fine distinction, yet it is one on which a good deal of reliance can be placed after considerable experience. In iodine the distinction of colour still persists, though it cannot be expressed in quite the same terms. The cytoplasm of the *E. coli* cyst is uniform and its granulations small and regular. In *E. histolytica* cysts there is a greater irregularity in the cytoplasm. Not only does the *E. histolytica* cyst more often contain chromatoid bodies and vacuoles, but the granulation of the cytoplasm itself is less uniform than in *E. coli* cysts. Taken altogether the cytoplasmic characters are of great importance in diagnosis.

### 4. *The chromatoid bodies*

Chromatoid bodies occur more frequently in *E. histolytica* cysts, and in these are characteristically rod-shaped. They are less frequent in *E. coli* cysts, and in these are much more irregular in shape, being divided, splintered, or laminated. Regular oblong

chromatoid bodies are very rare in *E. coli*, and even when present are usually needle-like, i.e., longer and narrower than the rod-shaped chromatoid bodies of *E. histolytica* cysts.

#### 5. *The vacuoles*

Vacuoles are more frequent in *E. histolytica* cysts, and as a rule, as Dobell and Jepps (1917) have pointed out, take on a paler colour in iodine than do the vacuoles of *E. coli* cysts. They are also, as a rule, less sharply outlined than in *E. coli* cysts. There are, however, fairly frequent exceptions to these generalisations.

#### 6. *The cyst wall*

The wall of the cyst of *E. coli* is thicker than that of the *E. histolytica* cyst. This point is, however, in my opinion not of much practical value, the thickness of the wall being so difficult to measure or estimate that very little diagnostic value can be attached to it. In common with Dobell and Jepps (1917), I can attach no meaning to the assertion made by some authors, e.g., Brug (1917), that the wall of the cyst of *E. coli* has often a double contour, while in *E. histolytica* the contour is single.

The greatest difficulty of diagnosis has arisen in my experience over tetranucleate and occasionally binucleate cysts without chromatoid bodies or vacuoles. In their absence the sole points of distinction are the colour and uniformity of the cytoplasm and the greater or smaller amounts of chromatin in the nucleus. Both these last distinctions may break down and the individual cyst be undeterminable.

In practice, as the sequel will show, the difficulty is not great, for the study of cases passing *E. coli* cysts only has shown that the tetranucleate cyst is very infrequent in undoubted *E. coli* infections, and in the vast majority of cases, even in mixed infections of the two species, the tetranucleate cyst has the characters of *E. histolytica*.

It may perhaps be well to sum up in parallel columns the points used in diagnosing the cysts of the two species. At the end of the paper a similar table will be given showing how the measurements of the present paper enable a more precise list of diagnostic points to be drawn up.

	<i>E. histolytica</i> cysts	<i>E. coli</i> cysts
No. of nuclei ... ..	1 to 4 ... ..	1 to 16.
Character of nuclei ...	Peripheral chromatin of small granules, more or less evenly distributed. Nuclei in consequence less distinctly visible	Peripheral chromatin of larger unevenly distributed masses. Nuclei, therefore, more distinctly visible
Cytoplasm ... ..	Colour greenish, typically not uniform in appearance	Paler, greyish, typically uniform in appearance
Inclusions ... ..	Chromatoid bodies more frequent, typically rod-shaped, with square or rounded ends. Vacuoles more frequent, one or more in the cyst, usually faintly stained by iodine, with less sharply defined edges	Chromatoid bodies less frequent, irregular in shape, with pointed or splintered ends. Vacuoles less frequent, generally single in the cyst, usually deeply stained by iodine, and with more sharply defined edges
Cyst wall ... ..	Thinner ... ..	Thicker

Using these criteria I found it impossible to diagnose only eighteen cysts in obtaining the two thousand whose measurements are given in the two principal curves of the present paper. As the work was done by one person only, there was no checking of the diagnosis by another observer, but I believe that the proportion which need be diagnosed as doubtful by an experienced observer is very small.

The morphological differences summarised in the above table have been figured by various authors. The plate accompanying Matthews' (1918) paper in the present number of this journal illustrates them well. For differences in the character of the nuclei, for instance, cf. figs. 5, 6 and 8 (*E. histolytica*) with figs. 15, 16 and 14 (*E. coli*). The difference in the structure of the cytoplasm is seen on comparing figs. 5 and 6 with figs. 16 and 17. The two types of chromatoid bodies are shown in figs. 9 and 18, while the vacuoles are contrasted in figs. 5 and 6 as compared with fig. 15.

## THE SIZE OF THE CYSTS

*Frequency curves for the cysts of E. HISTOLYTICA and of E. COLI*

The cases for examination were taken at random from the material examined by routine during the ten months of the work. It was thought that thus a sufficiently large number of the cysts (say 1,000) being taken from a sufficient number of cases, curves would be obtained representative of the two species.

*The curve for E. HISTOLYTICA*

We will consider first the frequency curve for the cysts of *E. histolytica*. The curve is given in fig. 1, p. 39, and represents the following measurements:

Scale-divisions	...	3.2	3.7	4.2	4.7	5.2	5.7	6.2	6.7
Number of cysts	...	2	17	71	65	36	8	60	156

Scale-divisions	...	7.2	7.7	8.2	8.7	9.2	9.7	10.2	10.7
Number of cysts	...	264	157	110	34	11	8	4	3

The thousand cysts whose measurements are shown in the curve were obtained from thirty cases. No case has contributed less than ten or more than fifty measurements to the total shown in the curve. Thus, although the contributions of all the cases are not the same, yet no one case predominates to any great extent over the others. The exact number of cysts from each case and their average diameter are given in Table I in ascending order of size.

The curves throughout this paper have the diameter of the cysts in  $\mu$  as abscissae and the numbers of cysts as ordinates. The cysts were grouped first in groups of half a scale-division, i.e.,  $0.85\mu$ , and the curves were drawn with this figure as the unit for the abscissae. The readings in  $1\mu$  units were substituted for the  $0.85\mu$  unit after the curves were drawn, and it is for this reason that the points on the curve so rarely correspond to an exact number of  $\mu$ . Cysts which were spherical had their diameter recorded in a single measurement. In the case of non-spherical cysts, their longest and

TABLE I.

No. of case	Number of cysts measured	Average diameter ( $\mu$ )
1	43	7.1
2	31	7.3
3	27	7.9
4	37	7.9
5	43	8.0
6	13	8.3
7	15	11.6
8	27	11.7
9	33	11.9
10	19	11.9
11	24	12.0
12	22	12.0
13	39	12.1
14	50	12.1
15	27	12.2
16	39	12.2
17	28	12.3
18	50	12.3
19	50	12.3
20	30	12.4
21	29	12.4
22	29	12.4
23	28	12.5
24	50	12.6
25	20	12.6
26	37	12.6
27	50	12.7
28	11	12.8
29	49	13.6
30	50	14.3
Total ...	1,000	



shortest diameters were both measured and the average of the two was taken as the diameter of the cyst. It should be noted that, wide as is the range of variation in the diameter of the cysts, the volume and weight of the cysts show an even wider range of difference, being proportional to the cube of the diameter. Thus, for example, the diameter of the largest cyst of *E. histolytica* measured ( $18\mu$ ) is approximately three and a quarter times the diameter of the smallest cyst measured ( $5.5\mu$ ). The actual size (volume) of the former cyst is, however, approximately thirty-five times that of the latter.

The extreme measurements are, as has just been stated,  $5.5\mu$  and  $18\mu$  for *E. histolytica* cysts. Dobell and Jepps (1917) have given  $5\mu$  and  $20\mu$  as the extremes, Wenyon and O'Connor (1917) record cysts of  $6\mu$  to  $18\mu$ , numbers which agree well with my own. As always, however, the extremes occur but rarely, and the essential point of interest is the distribution of the sizes between the two extremes. A most important feature of the curve is that it is bimodal. There is, moreover, a very marked separation between the two portions of which the curve consists. The first portion, with mode at  $7.1\mu$ , contains 193 cysts and their average diameter is  $7.68\mu$ . The second portion, with mode at  $12.2\mu$ , contains 807 cysts and their average diameter is  $12.58\mu$ . There seems to be no doubt from the curve that the cysts of this species divide themselves naturally into two strains, differing only in size, with dimensions as indicated in the curve. The smaller strain has been recognised recently (see James (1914), Woodcock and Penfold (1916), Wenyon and O'Connor (1917)), and a full account of it is given by Dobell and Jepps (1917). In my experience, cysts with diameters of  $9.5\mu$  and thereabouts, i.e., intermediate between the two strains, are very rare, as shown by the curve. I have encountered no case with cysts whose average diameter lies between  $9\mu$  and  $10\mu$ , nor any case showing even a considerable number of such cysts. The few cysts with diameters between  $9\mu$  and  $10\mu$  recorded in the curve are at the extreme limit of the range of size shown by the infections comprising them. They are either the very largest cysts of infections of the 'small' strain or the smallest cysts of infections of the 'ordinary' strain. Wenyon and O'Connor (1917), however, record one case (Kettlewell) most of whose cysts were  $9\mu$  to  $10\mu$  in diameter, and

the average diameter of fifty of whose cysts was  $9.2\mu$ . If such cases were at all frequent the curve given in fig. 1 would take on a very different appearance, for the separation between the two parts of the curve would be obliterated and the 'small' strain thus be no longer distinct from the 'ordinary' strain. Such infections must, however, be extraordinarily rare. The general agreement of all the older observations, that the lower limit of size for *E. histolytica* cysts was  $10\mu$  (see, for example, Elmassian (1909), Wenyon (1915), Kuenen and Swellengrebel (1913)), could scarcely have been reached if infections with an average size of about  $9\mu$  were at all common. In the thirty infections in my curve there was no such case, nor did such a case appear among the cases omitted from my curve because of the small number of measurements in each, nor in the infections which I have measured since the figures of this curve were completed. These infections number fifty in all, and had been acquired in various regions of the globe.

There is therefore *prima facie* evidence that a 'small' strain and an 'ordinary' strain exist differing from each other in size. They are not distinguished from each other in any other morphological feature, nor, as far as is known, in any respect save size. The subject of size strains will be discussed somewhat more fully later. The proportion of the 'small' strain in the curve obviously depends upon how many infections of this strain have been set aside for measurement. In this respect, records show that in a period when the greater part of this work was done there were among seventy-five infections of *E. histolytica* found in the routine examinations twenty-one of the 'small' strain, i.e., 28 per cent. Table I shows that of the thirty infections included in the curve, six (20 per cent.) were of the 'small' strain. Of the 1,000 cysts in the curve, 193, or 19 per cent., were of the 'small' strain. This strain has therefore a somewhat smaller representation in the curve than it is entitled to. There is no doubt, however, that the salient features of the curve would have been substantially the same if the representation of the two strains had been in strictly accurate proportions.

Treating separately the part of the curve which refers to the 'ordinary' strain, the following facts may be recorded. The curve is not a typical symmetrical frequency curve, in which the mode and the mean coincide, but extends further on the right of the mode than

on the left. The average diameter of the 807 cysts represented in it is  $12.6\mu$ , while the mode is at  $12.2\mu$ . The point representing the mode in the curve is of course really an average for the group  $11.8\mu$ — $12.65\mu$ , and is more accurately represented by a horizontal line. The asymmetry of the curve is indicated in the fact that the average is at the right hand end of this modal group of measurements. With regard to the fact that the curve extends further to the right of the mode than to the left, it is worth noting that, of the twenty-eight cysts with diameters above  $15\mu$ , eighteen were contributed by one case alone (Case 30), whose average measurement is very high ( $14.3\mu$ ). Not only is the curve for the 'ordinary' strain asymmetrical, but it is not so regular as would be expected for a curve containing 800 measurements. Further reference will be made to this point. The curve for the 'ordinary' strain has a probable error of  $\pm 0.86\mu$ .

#### *The curve for E. COLI*

The curve for 1,000 *E. coli* cysts is given in fig. 2, p. 39, and represents the following measurements:

Scale-divisions ...	...	7.3	7.8	8.3	8.8	9.3	9.8	10.3	10.8	11.3	11.8
Number of cysts	...	1	23	51	125	143	173	145	111	93	56

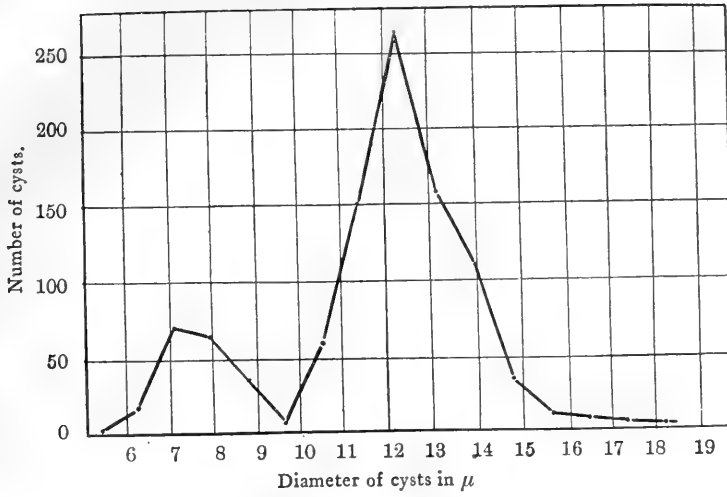
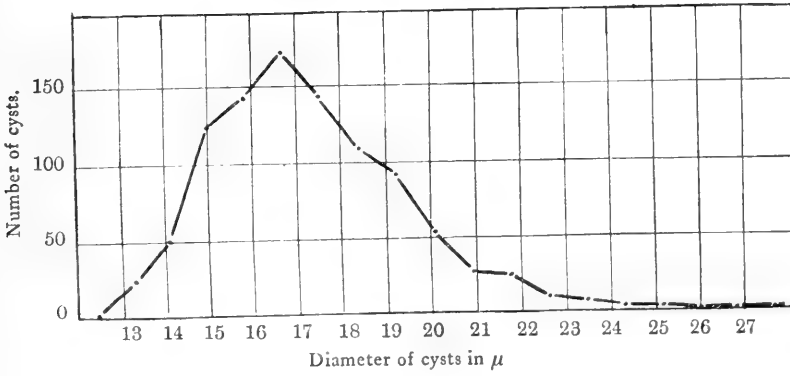
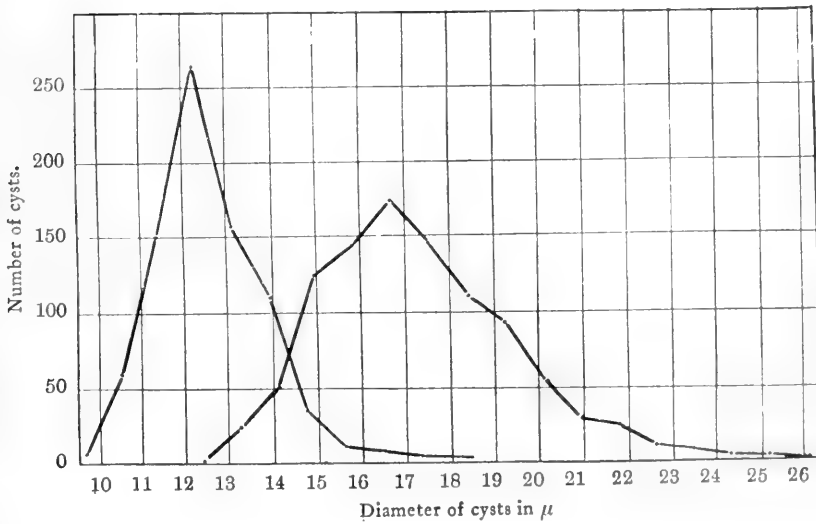
Scale-divisions ...	...	12.3	12.8	13.3	13.8	14.3	14.8	15.3	15.8	16.3	...
Number of cysts	...	28	24	10	8	3	3	1	1	1	...

The cases from which the 1,000 *E. coli* cysts represented in Fig. 2 were obtained are shown in Table II, where they are arranged in ascending order of size.

The curve for *E. coli* differs from the curve for *E. histolytica* in being unimodal with mode at  $16.7\mu$  or, rather more accurately, the modal group is  $16.25\mu$  to  $17.1\mu$  with centre at  $16.7\mu$ . There is no clear indication in the curve of more than one strain being present in the cysts of this species. The extreme measurements are  $12.5\mu$  and  $27.5\mu$ . Apart from this series of measurements the writer has a

TABLE II.

No. of case	Number of cysts measured	Average diameter ( $\mu$ )
1	22	15.5
2	12	15.6
3	51	15.6
4	50	15.8
5	30	16.0
6	17	16.1
7	33	16.2
8	25	16.3
9	50	16.3
10	50	16.4
11	19	16.7
12	50	16.8
13	14	16.8
14	10	16.9
15	10	17.1
16	50	17.4
17	26	17.4
18	10	17.5
19	51	17.5
20	50	17.6
21	10	17.7
22	13	17.8
23	19	17.9
24	13	18.1
25	20	18.5
26	50	18.6
27	50	18.6
28	50	18.8
29	34	19.0
30	11	19.2
31	11	20.0
32	36	20.1
(14 cases Miscellaneous)	53	16.8
	Total 1000	General average 17.3

FIG. 1. 1000 cysts of *E. histolytica*.FIG. 2. 1000 cysts of *E. coli*.FIG. 3. *E. histolytica* 'ordinary' strain 807 cysts. *E. coli* 1000 cysts.

record of a cyst of *E. coli* measuring  $34\mu$  in diameter. These extremes agree fairly closely with those recorded by Dobell and Jepps (1917), and also with those cited by them from other authors. I have not observed any cyst of *E. coli* as small as  $11\mu$ , the smallest size recorded by Dobell and Jepps, but have no doubt that in a very extensive series of measurements *E. coli* cysts of this size might occur. They must, however, be very rare. Although the largest cysts extend to  $25\mu$  or  $30\mu$ , and even very rarely beyond this, yet the curve shows clearly that cysts beyond  $22\mu$  are very infrequent. Ninety-seven per cent. of all the cysts in the curve are  $22\mu$  or below in diameter. The curve for *E. coli* is like that for *E. histolytica* in being somewhat asymmetrical. While the mode is at  $16.7\mu$  the average of the 1,000 measurements is  $17.3\mu$ , i.e., it does not lie in the modal group of measurements at all. The curve is even less regular than the *E. histolytica* curve, and certainly less so than might be expected from so large a number of measurements as 1,000. The probable error of this curve is  $\pm 1.49\mu$ .

*Overlapping curves of E. HISTOLYTICA and E. COLI*

A study of the two previous curves drawn so as to overlap each other, fig. 3, p. 39, brings out a point of great importance, namely, the value of size as a criterion of the species. It is seen at once that the curves overlap each other from  $12.5\mu$  (the smallest measurement of *E. coli*) to  $18\mu$  (the largest measurement of *E. histolytica*). According to Dobell and Jepps (1917) these extreme points may be even extended by a wider series of observations to  $11\mu$  and  $20\mu$ . It might be at once deduced that for all cysts between  $11\mu$  and  $20\mu$  in diameter size is useless as a diagnostic character, as cysts between these extremes may be either *E. coli* or *E. histolytica*. While this deduction may be strictly correct in an absolute sense, yet a study of the curves will show that these limits may be reduced very much and yet the diagnosis from size may have a very high probability of accuracy. It is really only between  $13\mu$  and  $15.5\mu$  that any considerable numbers of both species of cysts occur. Below  $13\mu$  there is a very high probability in favour of *E. histolytica*, above  $15.5\mu$  the probability is very high in favour of *E. coli*. Thus at a diameter of  $16.7\mu$  the chances are 25 : 1 (approximately) that any cyst will

be *E. coli*.\* Similarly the chances are 75:1 (approximately) in favour of a cyst of  $12.5\mu$  being *E. histolytica*.\* Contrasted with this we find that the chances are even that a cyst of  $14.3\mu$  is *E. histolytica* or *E. coli*. It is therefore quite justifiable, except between the fairly narrow limits  $13\mu$  to  $15.5\mu$ , to allow considerable weight to size as a diagnostic character, and this result is one of the most important deductions from the present series of measurements.

Although the sizes of individual cysts of the two species are often coincident, yet it may be worth while to point out that, if averages of fifty cysts are taken, the two species do not overlap, so far as my measurements go. The highest average measurement that I have obtained for a sample of 50 or more cysts of *E. histolytica* is  $14.3\mu$ . Wenyon and O'Connor (1917) give one case in which fifty cysts of *E. histolytica* averaged  $15.1\mu$ . Even this, however, is smaller than my lowest average for *E. coli*, which is  $15.6\mu$  for a sample of fifty-one cysts. Though further research may reveal *E. coli* infections whose average diameter is smaller than this, yet it can be said that, so far as the present evidence goes, the average diameter of fifty cysts is always distinctive of the species. Of course, in practice this statement is not of any great value, as the measurement of fifty cysts in every doubtful case would be laborious or even impossible. It would in any case give no help in the case of a mixed infection.

### THE SHAPE OF THE CYSTS

It is well known that both in *E. histolytica* and in *E. coli* the cysts are usually more or less spherical. Cysts occur, however, in both species in which the shape is not spherical but ovoid or more or less elongated. When such a lack of symmetry was obvious in cysts occurring in the present series of measurements, the size of the cyst was expressed by the mean of its longest and shortest diameters. The difference between these two diameters in the cysts thus obviously not spherical varied very much. Sometimes it was

\* These chances apply to a series of cases in which *E. histolytica* infections and *E. coli* infections are equally common. In the usual series of cases of convalescent dysenteries where *E. coli* infections are about twice as common as infections of *E. histolytica* the chances would be 50:1 and 37:1 respectively.

small. Some of the records show a difference of  $0.33\mu$  between the two diameters, while differences of  $0.5\mu$  and  $0.8\mu$  are commonly recorded. On the other hand, the cyst may be very much elongated, the extreme record showing a difference of  $9\mu$  (approximately) between the two diameters in the case of a cyst of *E. coli*. No doubt if very carefully examined, and if differences smaller than those here recorded were noted, a very large percentage of the cysts would be found to be not perfectly spherical. The following figures refer to cysts in which the asymmetry was obvious. These in practice included all those cysts in which the two diameters differed by  $0.5\mu$  or more, and even some which differed by as little as  $0.33\mu$ .

Of 1,233 cysts of *E. histolytica* measured for this record, 260 were definitely recorded as asymmetrical, a percentage of 21. The extreme of asymmetry in *E. histolytica* was reached in this series of observations in the case of a cyst measuring  $18.7\mu$  by  $11.6\mu$ , a difference of  $7\mu$  between the longest and shortest diameters. Other extreme records are  $17\mu$  by  $10.5\mu$  (difference  $6.5\mu$ ),  $15.5\mu$  by  $9.5\mu$  (difference  $6\mu$ ), and  $15\mu$  by  $9.5\mu$  (difference  $5.5\mu$ ). Individual infections vary very much in their relative asymmetry. In one infection twenty-seven cysts were measured without any asymmetrical cyst being recorded, in another only two asymmetrical cysts were noted in twenty-eight, while on the other hand an infection occurred in which twenty-one cysts were recorded as asymmetrical out of forty-five measured, or very nearly 50 per cent. There is some evidence that these differences persist and are characteristic of the different infections, but there is not as yet sufficient proof of this.

In the case of *E. coli*, 1,170 cysts were measured, and 193 of these (16.5 per cent.) were asymmetrical. This is lower than the corresponding figure for *E. histolytica* cysts, thus confirming the statement of Wenyon (1915) that the cysts of *E. histolytica* 'are not so accurately spherical as those of *E. coli*.' Differences of  $0.33\mu$  and  $0.5\mu$  between the diameters of *E. coli* cysts are recorded, while at the other extreme are records of cysts  $26\mu$  by  $17\mu$  (difference  $9\mu$ ),  $27\mu$  by  $19\mu$  (difference  $8\mu$ ), and  $23\mu$  by  $15\mu$  (difference  $8\mu$ ). As instances of differences in the records of individual infections there may be given one case where no asymmetrical cyst was recorded out of fifty measured, while in another case twenty-seven were asymmetrical out of seventy-five measured.



## THE NUMBER OF NUCLEI IN THE CYSTS

1. *E. histolytica*

As it seems clear that two size strains of cysts exist in the species *E. histolytica*, the two will be considered separately in the remarks which follow.

TABLE III.

<i>E. histolytica</i> 'ordinary' strain				<i>E. histolytica</i> 'small' strain		
Number of nuclei in the cyst	Number of cysts	Percentage of total	Average diameter in $\mu$ with probable error	Number of cysts	Percentage of total	Average diameter
1	326	32.2	$12.74 \pm .05$	82	45.0	7.5
2	136	13.4	$12.55 \pm .08$	53	29.1	7.5
3	13	1.3	12.30	1	...	...
4	536	53.0	$12.40 \pm .03$	46	25.3	7.8
Total	1011	...	...	182	...	...

Table III gives the results of observations of the number of nuclei present in each cyst. The 1,011 cysts of the 'ordinary' strain in the table include a number which are not included in the curve previously given of cyst diameter. They do not, however, include all those given in that curve. In spite of certain omissions and additions the material is substantially the same as that already dealt with. It is clear at once from Table III that, as is well known, the mature tetranucleate cyst of *E. histolytica* is accompanied in the faeces by considerable numbers of the mono- and bi-nucleate cysts. A little over half of all the cysts encountered were tetranucleate. The mononucleate cyst comes next in frequency, making up about one-third of all the cysts. The stage with three nuclei is very rarely encountered, only occurring in about one per cent. of the cysts. The 'small' strain shows some differences from the 'ordinary' strain in the incidence of the various nuclear stages, but too much importance must not be attached to the figures in this part of the table which represent much smaller numbers of cysts.

Table IV gives the particulars for 1,132 cysts of *E. coli*. The outstanding feature of the table is the enormous preponderance of eight-nucleate cysts in the total. Though every experienced observer has known that eight-nucleate cysts were encountered the most frequently, yet it is interesting to have a more exact idea of the extent of this preponderance. It must be at once stated that it occurs in cysts from stools which are for the most part formed or

TABLE IV.

<i>E. coli</i>			
Number of nuclei	Number of cysts	Percentage of total	Average diameter ( $\mu$ )
1	6	...	17.7
2	77	6.8	17.3
3	8	...	17.5
4	31	2.7	17.3
5	4	...	18.1
6	7	...	17.3
7	5	...	18.3
8	983	86.8	17.4
12	2	...	23.7
16	9	1.0	23.4
Total ...	1132		

semi-formed. It is well known, and I have been able to confirm the fact by notes taken on several cases, that in loose stools the stages with a smaller number of nuclei are more frequent, as also are the amoebae. Thus Case 26 of Table II had a heavy and persistent infection of *E. coli*. The cysts of this infection were observed on six different dates. On three of these occasions the stool was loose after administration of a saline purgative. On the other three the stool was formed. The following results were obtained:—

Number of nuclei ...	1	2	3	4	5	6	7	8	16	Total
In the formed stools	...	3	2	3	...	...	1	115	...	124
In the loose stools	1	15	1	3	...	1	...	40	1	62

In the formed stools the cysts with eight nuclei or more make 93 per cent. of the total. In the loose stools those with eight or more nuclei make only 66 per cent. of the total. Though, even in the loose stools the eight-nucleate cysts are in the majority, yet they do not show such a great preponderance as in the formed stools. In formed and semi-formed stools, then, as Table IV shows, the eight-nucleate cysts form 87 per cent. of all the cysts seen. Two consequences of importance in diagnosis follow: (1) The rule that all cysts with more than four nuclei are diagnosed as *E. coli* becomes of very great practical value. In similar material to my own, 89 per cent. of the *E. coli* cysts can at once be certainly diagnosed. Forty-one samples of over ten cysts each were examined from a series of thirty-one cases. Of these, eleven samples of 10, 13, 50, 12, 32, 10, 10, 50, 16, 32 and 20 cysts, respectively, were entirely composed of eight-nucleate cysts. In addition to these, five other samples of 30, 20, 20, 24 and 25 cysts, respectively, were entirely composed of cysts with more than four nuclei. Not one of the samples was altogether without eight-nucleate cysts, and of course in almost all, these were in the majority. (2) The general impression of *E. coli* cysts obtained from such material as was used for this work is based overwhelmingly upon the mature cyst, the eight-nucleate cyst. In *E. histolytica* one's general impression is obtained from mononucleate and binucleate cysts as well as from the mature tetranucleate cyst. It is certain that if mononucleates and binucleates were numerous among *E. coli* cysts, a different impression of the cysts of the species would be obtained. The following instances of this may be given from the diagnostic table earlier in the paper:

*E. coli* cysts

*Colour paler, greyish.* If binucleate cysts were common or in preponderance this distinction of colour might have to be given up or more lightly stressed. Often the colour of the binucleate *E. coli* cyst, and particularly of the vacuolated binucleates, approaches very nearly to that of the *E. histolytica* cyst. It is the eight-nucleate cyst in particular which has the paler colour.

*Cytoplasm more uniform.* The typical uniform cytoplasm is best seen in the eight-nucleate cyst, though it occurs also in every stage.

*Vacuoles less frequent.* If mononucleate and binucleate *E. coli* cysts were common this distinction would certainly disappear, for in these stages the cyst is very frequently vacuolated. Probably the majority of such cysts are vacuolated.

The average diameter of the cysts at all stages of nuclear division is given in the last column of Table IV. There is no significant difference in any stage until one comes to the cysts with more than eight nuclei. Although these are few in number, yet the very large difference (about  $6\mu$  greater) in their average diameter from that of the cysts with eight nuclei or less is certainly significant. They seem to be in some way monstrous or abnormal forms.

Inspection of Tables III and IV shows that those stages of nuclear division which involve the absence of simultaneous division of all the nuclei in the cyst are rare. This is particularly marked in cysts of *E. histolytica* where only about one per cent. of all the cysts encountered were three-nucleate. In *E. coli* cysts the stages which show that all the nuclei of the previous stage have not divided simultaneously are those with three, five, six, seven and twelve nuclei respectively. It is to be noted that when these numbers of nuclei occur in the cyst, one or more of the nuclei are usually larger than the rest, the larger ones being presumably those which have lagged behind the others in division. These stages are all encountered very infrequently, in less than 1 per cent. of the cysts in each case. It is noticeable, however, that the stages with two and four nuclei are not very common either, being found in approximately 7 and 3 per cent. only of the cysts, respectively. The four-nucleate stage is only about four times as common as the three-nucleate stage, the one probably indicating simultaneous and the other certainly showing successive division of the two nuclei of the previous binucleate stage.

The seventy-seven cysts of *E. coli* in the binucleate stage are of two kinds, vacuolated and non-vacuolated. These two kinds are illustrated in the plate accompanying Matthews' (1918) paper, figs. 15 and 16. Of the vacuolated kind there were forty-one, of the non-vacuolated thirty, while in six there is no record as to this point. Twenty-eight of the thirty-one tetranucleate cysts were non-vacuolated. It is thus seen that the number of non-vacuolated binucleate cysts is approximately equal to the number of non-vacuolated tetranucleate cysts. This fact perhaps lends some support

to Wenyon and O'Connor's (1917) hypothesis that the peculiar vacuolated binucleate *E. coli* cyst is abnormal and not a part of the ordinary development. The vacuolated cysts are those which provide the extra number of binucleates over the tetranucleates, and they possibly do not develop further. The great scarcity of mononucleate *E. coli* cysts in my material is noteworthy. In the case in which the largest number of *E. coli* cysts was measured, the pre-cystic forms were binucleate. It is possible that this is very generally the case, and that the first division of the nucleus usually takes place before encystment. Further observation of infections in which numerous precystic forms and immature cysts are present is necessary to settle this point.

### THE CHROMATOID BODIES

These are undoubtedly more prevalent in *E. histolytica* cysts than in *E. coli* cysts. Of 1,162 cysts of the 'ordinary' strain of *E. histolytica* (my data for the presence or absence of chromatoid bodies in the cysts of the 'small' strain are very incomplete, but I have seen nothing which leads me to think that this strain differs from the 'ordinary' strain in respect of chromatoid bodies) chromatoid bodies were present in 319 (27 per cent.), absent in 760 (65 per cent.), and doubtful in 83 (8 per cent.). The cysts with chromatoid bodies were, however, well distributed through the cases. Samples of ten cysts or more were observed from twenty-nine different cases. In only four cases did the samples throughout show no cysts containing chromatoid bodies. Samples of ten or more cysts were examined from forty-eight different stools from these cases. In ten of these samples there were no cysts with chromatoid bodies. In practice, therefore, one sees chromatoid bodies in the majority of infections where fair numbers of cysts can be examined. If only one to five cysts are seen, however, they may very often show no chromatoid bodies. Samples of fewer than ten cysts were examined from twenty-seven different stools from the present series of cases. Seventeen of these samples were entirely without chromatoid bodies. Since scanty infections in which one cannot observe more than ten cysts without great labour are fairly common, one quite frequently must diagnose in practice without the aid of chromatoid bodies. The infections so far referred to were examined primarily with the object of measuring the diameter of the cysts. They were selected

infections in which cysts were more abundant than the average. In order to have figures bearing upon the average infection as met with in routine examinations, a further series of observations was made on all the infections of *E. histolytica* appearing in the routine examinations over a certain period. These were examined in saline, in which medium the chromatoid bodies are more distinctly seen than in iodine. Notes were made of the abundance of cysts in the infection and whether chromatoid bodies were absent or present in the sample examined, also, if present, whether the cysts containing them were a majority or a minority of the cysts present. The following results were obtained. Samples were taken from one hundred and forty-four different stools from twenty-three different cases. In 51 per cent. of these samples the cysts were entirely without chromatoid bodies. In 28 per cent. the cysts containing them were fewer than half of the whole number observed, in 11 per cent. about half the cysts contained chromatoid bodies, and in 10 per cent. the cysts containing chromatoid bodies were in the majority. The samples examined were of the size usually seen in our routine examinations, i.e. they comprised in each case all the cysts present under two coverslips. It appears from this that in routine examinations there are just about equal chances of infections without any chromatoid bodies being encountered as of those in which chromatoid bodies are present. The following table shows the actual figures for some of the cases examined most often. Only one sample was taken from each stool.

TABLE V.

Case	Number of samples without chromatoid bodies	Number of samples in which fewer than half the cysts have chromatoid bodies	Number of samples in which about half the cysts have chromatoid bodies	Number of samples in which cysts with chromatoid bodies are in the majority
1	15	5	...	1
2	5	3	2	2
3	5	1	1	5
4	6	1	1	...
5	10	11	1	1
6	9	10	2	...

Only once in both series of observations, i.e. the series in iodine as well as the series in saline, was an infection encountered in which every cyst observed contained chromatoid bodies.

It is possible that in cysts containing very small chromatoid bodies these might be overlooked in iodine, and that only counts from stained preparations would give absolutely accurate results. It is, however, from saline or iodine preparations that the usual routine diagnosis has to be made, and to such cases the present observations are applicable.

Of the three hundred and nineteen *E. histolytica* cysts containing chromatoid bodies 30 per cent. were mononucleate cysts, 19 per cent. were binucleate cysts, and 50 per cent. were tetranucleate cysts. The cysts themselves occur, as Table III shows, in the proportions mononucleate cysts 32 per cent., binucleate cysts 13 per cent., tetranucleate cysts 53 per cent. The fairly close agreement between these figures seems to show that the supposition of some writers (Hartmann\* 1912, James† 1914) that chromatoid bodies tend to disappear as the cyst becomes mature is not borne out by the facts. The chromatoid bodies seem indeed to be present indiscriminately in all the stages.

Chromatoid bodies are undoubtedly less frequent in cysts of *E. coli*. Out of 1,240 cysts observed during the course of this work 1,159 (93 per cent.) were without any chromatoid bodies. In sixty-nine (5·5 per cent.) chromatoid bodies were present. The sixty-nine cysts with chromatoid bodies came from nine different cases out of the forty-six cases observed, so that at one time or another about 20 per cent. of all the cases with an infection of *E. coli* showed cysts with chromatoid bodies. All the cysts with chromatoid bodies were eight-nucleate cysts with one exception (a tetranucleate cyst).

The general result of these observations is to diminish the value of chromatoid bodies as a diagnostic character for *E. histolytica* cysts because they are so frequently absent from the cysts (two-thirds

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\* Hartmann states, 'Die Bedeutung dieser Chromidien und Chromidialkörper ist nicht vollkommen klar. Wahrscheinlich handelt es sich um einen Reservestoff; denn im weiteren Verlauf der Cystenbildung und der sich anschliessenden Cystenruhe werden diese Körper in der Regel ganz oder fast ganz aufgebraucht.'

† James says, that in many of the adult cysts there are but few chromidia, and the four nuclei show very plainly.

of all the cysts being without them), at any rate when observed in saline or iodine. It has been shown also that in such samples as are commonly taken for routine examination the whole sample is without chromatoid bodies on about 50 per cent. of the occasions of examination.

With the conclusions here reached as to chromatoid bodies may be contrasted the statements of Mathis and Mercier (1917*a*). These authors state that the typical mature (tetranucleate) cysts of *E. histolytica* always contain chromatoid bodies and that such typical cysts are 75 to 80 per cent. of all the cysts encountered. My observations show that of tetranucleate cysts, as of mononucleate, only about 25 per cent. contain chromatoid bodies.

### SIZE STRAINS IN THE TWO SPECIES

We have seen already that the frequency curve for *E. histolytica* cysts indicates the existence of two strains differing in size, which I have referred to in this paper as the 'small' strain and the 'ordinary' strain respectively. These two strains have already been noted in previous literature. Wenyon and O'Connor (1917) and Dobell and Jepps (1917)\* have carried this idea further, and have indicated the existence of other size strains. The evidence given is that when the average diameter of a number of cysts is obtained from any one infection, this average diameter remains constant, or nearly so, from day to day, for that infection, so that a sufficient

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\* While the present paper was passing through the press, a paper by Dobell and Jepps (1918) appeared in which the theory of the presence of various size strains in the species *E. histolytica* was much more fully elaborated. By the measurement of large samples (500 cysts) of seven different infections the authors claim to have established the existence of five size strains in this species. The cysts occurring with greatest frequency in each of these five races are approximately of the following sizes:  $6.6\mu$ ,  $8.3\mu$ ,  $11.6\mu$ ,  $13.3\mu$ , and  $15\mu$ . The measurements are the fullest and most accurate that have yet appeared, and I am in full agreement with their conclusion that infections of these sizes were found in the material on which they worked. It is probable, also, that the infections of the five different sizes mentioned correspond to five real strains or races in *E. histolytica*. I do not, however, think that, so far, the authors have given complete proof of this supposition. They say, 'For the complete demonstration of this fact [the existence of strains in *E. histolytica*] it is necessary to prove that the mean diameter of the cysts from any patient is not subject to any considerable variation from day to day, but remains constant.' In proof of this they appeal to their general experience, but only furnish actual measurements from one case, their E42. In this case two samples of 500 cysts each were taken at dates about a month apart, and the average diameter of the two samples differed by only  $0.25\mu$ . This difference and differences similarly obtained in my own work are very small compared with the difference between the two strains which I have called the 'small' ( $7.7\mu$ ) and the 'ordinary' ( $12.6\mu$ ), and I consider the existence of these two strains to be sufficiently established. The difference found by Dobell and Jepps, and differences similarly obtained



sample obtained at any time gives an average size characteristic of that infection and different from the average of other infections. Wenyon and O'Connor say: 'Starting from the strain with small cysts, a series of strains occur with gradually increasing average size of cyst. There are strains in which the cysts measure  $9\mu$  to  $12\mu$ , others  $10\mu$  to  $14\mu$ , others  $12\mu$  to  $16\mu$ , and finally large strains with cysts measuring  $14\mu$  to  $18\mu$ . As is to be expected, each strain is associated with "minuta" forms of amoebae of corresponding size. It seems very improbable that these strains represent different species of amoebae, for we cannot be sure that a strain of amoebae which will produce cysts of small size at one time will never at another time produce larger ones. We have noted, however, that in case Healy, in which cysts of large average size were found for a long time, towards the end of the period of observation a certain number of smaller ones began to appear. The point, however, can only be definitely decided by following individual untreated cases for long periods.'

In the course of the present work samples from different stools of certain individual cases were measured on several different occasions, and it might have been thought that in this way proof would have been forthcoming as to whether the average size of the cysts of an infection varied or not from time to time. It has to be remembered, however, that unless fairly large numbers of cysts are measured on each occasion the variations due to errors of sampling will be large, and no strict proof will be obtained. For the main purpose of this work large samples were not required, and as has been indicated, fifty cysts was usually the largest number measured at one time.

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by me on smaller samples are, however, not insignificantly small when compared with the difference between such strains as the  $11.6\mu$  and  $13.3\mu$  strains. It seems to me, therefore, that much more evidence than can be supplied by two samples from but one case, however large the samples may be, is necessary to prove the constancy of size of races as close together as this in average size. Successive random samples of 500 cysts from the same stool do not differ by as much as  $0.25\mu$ , so that such a difference, small as it is, may be significant of change rather than constancy. When, too, the authors suggest that further detailed work would no doubt reveal other races possessing cysts of other mean diameters, they are elaborating a system of strains within the species whose mean diameters are so near together that it becomes almost impossible to prove their existence. If it is taken as probable, rather than fully proven, that the five strains of Dobell and Jepps exist, there are indications that in the present work I have found, besides the 'small' strain, a strain corresponding to the  $11.6\mu$  strain of Dobell and Jepps in my Infection I of Table VII, shown in Fig. 4, and one corresponding to their  $13.3\mu$  strain in Infections 12, 13, and 14 of Table VII, shown in Fig. 7. It seems clear from my Infections 7 to 11 of Table VII that either a race intermediate between these two exists or that many infections consist of the  $11.6\mu$  and  $13.3\mu$  strains in roughly equal proportions. I have found no infection with an average as high as  $15\mu$ .

TABLE VI.

Case	Date of examination	Number of cysts measured	Average diameter ( $\mu$ )
1	17.1.18	21	14.4
	19.1.18	33	13.9
	29.1.18	23	13.4
	25.2.18	60	13.7
2	13.12.17	45	11.6
	21.1.18	25	11.4
	22.1.18	30	11.8
3	1.12.17	37	12.6
	16.2.18	50	12.0
4	2.7.17	50	12.3
	16.7.17	28	12.6
5	25.7.17	20	12.2
	10.8.17	19	12.1

Table VI gives for five cases of *E. histolytica* the average diameter of the cysts at different dates in the same case, together with the number of cysts measured. Mere inspection, however, does not enable us to decide how far the variations which occur in the average diameter are significant. In Cases 2, 4 and 5 the agreement seems close, while it is somewhat less so in Cases 1 and 3, but one cannot tell whether these differences are, or are not, due to random errors of sampling in such small numbers. I have applied Karl Pearson's (1911) method of 'goodness of fit'\* to Cases 1 and 3. By this method it is found that the variations in Case 1 are such as are to be expected in samples of this size. In Case 3 the difference is such that only once in fifty trials would such a difference occur without real change in the size of the cyst population. The apparent change in average size in Case 3 appears therefore to be significant, but much further work on these lines is necessary before this point can be settled. It is interesting, apart from definite proof on this point, to see if any indications occur in my measurements pointing to the existence of a greater number of size strains than the two already mentioned.

In Table VII are found in ascending order of size the average diameters of all samples of cysts larger than fifty of the 'ordinary' strain.

\* I am much indebted to Dr. James Johnstone for drawing my attention to this method and for other help with the statistics of this paper.

TABLE VII.

Infection	Number of cysts measured	Average diameter of the cysts ( $\mu$ )
1	100	11.6
2	50	11.7
3	60	11.8
4	50	11.9
5	51	12.1
6	87	12.2
7	92	12.4
8	73	12.4
9	63	12.6
10	51	12.7
11	80	12.7
12	49	13.6
13	140	13.8
14	55	14.3

It would be expected, if strains exist among these, that the averages would tend to group themselves round two or three nodal points according to the number of strains existing. Instead of this, however, we find a continuous series of eleven infections from 11.6 $\mu$  to 12.7 $\mu$ . Then comes a distinct break in the series, the remaining three infections having averages of about 1 $\mu$  higher than the highest of the previous eleven infections. There is some indication therefore of two strains in this series, a larger and a smaller.

Fig. 4, p. 57, shows the curve of frequency of one of the smaller infections (average 11.6 $\mu$ ) and also the curve for one of the larger infections (average 13.8 $\mu$ ). The measurements represented in the curves are:—

Scale-divisions	...	...	...	...	5.7	6.2	6.7	7.2	7.7	8.2	8.7	9.2	9.7	10.2	10.7
Number of cysts	11.6 infection	...	...	...	3	17	37	26	12	5	...	...	...	...	...
	13.8 infection	...	...	...	...	...	1	11	34	38	33	16	5	1	1

The comparison seems to show clearly that the strains are different, there being a difference of about  $2\mu$  between the modes,  $1.5\mu$  between the minimal readings and about  $4\mu$  between the maximal readings. In each case, too, a fairly smooth and symmetrical curve is produced. These infections are those shown in Cases 1 and 2 of Table VI, and it is seen that the variations from day to day are considerably smaller than the difference between the average of one curve and another. If the readings from the two infections, however, are added together, the curve of fig. 5, p. 57, is obtained with mode at  $13.1\mu$ . This curve, too, if smoothed a little between the third and fourth reading becomes a typical symmetrical frequency curve. When, therefore, it is remembered that between these two infections there are many others of intermediate sizes, it will be seen that the proof of the existence of two separate strains corresponding to the two infections in fig. 4 depends upon the most rigid proof that variations in the size of the cysts do not occur from one day to another which are at all significant in comparison with the difference in size between the two strains. Such proof is not yet forthcoming in this series of measurements, and the question must be left open for the present.

It may be recorded, however, that infections of the 'ordinary' strain\* of *E. histolytica* from those cases who have never been out of England and who have never had dysentery are prevaillingly of the smaller-sized cysts. In fig. 6, p. 57, the curve represents the measurements of all the cysts measured from carriers of *E. histolytica* who had never left England. The figures represented in the curve are:—

Scale-divisions ...	...	...	5.7	6.2	6.7	7.2	7.7	8.2	8.7
Number of cysts	...	...	5	43	85	95	47	22	3

It will be seen that a symmetrical curve results, with average of  $12\mu$  (300 cysts measured) and with no cyst over  $15\mu$ . The mode of the curve is at  $12.2\mu$  and the mean is  $12\mu$ , so that these coincide closely enough. What significance attaches to the fact that all the infections of the 'ordinary' strain which have come to my notice in persons who have never left England and who have not had

\* Infections of the 'small' strain are infrequent in carriers who have never left England.

dysentery are smaller than the average in size I cannot say. Further investigations are being made into this question.

In fig. 7, p. 57, the curve represents the measurements of the three infections with large cysts shown in Table VII. The figures shown in the curve are :—

Scale-divisions	5·7	6·2	6·7	7·2	7·7	8·2	8·7	9·2	9·7	10·2	10·7
Number of cysts	1	2	2	23	54	66	52	25	11	4	4

The curve is smooth and symmetrical, with mode  $13\cdot9\mu$  and mean  $14\cdot1\mu$ , and such as would be obtained if it represented a single strain. It was noted in describing the main curve (fig. 1) for the 'ordinary' strain of *E. histolytica* that it was not quite as smooth or symmetrical as it might have been expected to be, containing as it does the measurements of 807 cysts. Both the curves obtained by separating out certain cases from the large group, viz., the curves of fig. 6 and fig. 7 are smoother and more symmetrical (as is seen by the closeness of the mode to the mean) than the large curve of fig. 1. This would be the case if the curves of figs. 6 and 7 represented separate strains, while the large curve represented a mixture of strains. The facts about these curves may therefore be an indication that separate strains exist within the 'ordinary' strain, but of course they constitute no proof of this hypothesis.

The existence of the 'small' and the 'ordinary' strains is better grounded. The present large series of measurements has revealed very few cysts indeed intermediate in size between these two strains, and no single infection in which the majority of cysts are of this intermediate size. The variations which occur in the average size of the cysts of an infection (see Table VI) are small as compared with the difference between the average size of the 'small' strain  $7\cdot7\mu$  and that of the 'ordinary' strain  $12\cdot6\mu$ . Observations of many more cases than are included in the measurements of this paper show that cases with the 'small' strain show that strain persistently for a long time if they are not cured, and that the same applies to the 'ordinary' strain. The two strains do not replace each other.

To summarise this section, it has been shown that there are

indications that the ordinary strain of *E. histolytica* cysts may be further sub-divided into at least one smaller and one larger strain. No proof of the existence of these strains can be established until it can be shown that the size of the cysts in one infection does not vary outside the limits of sampling errors from one day to another. It would also be of great interest to know whether a change of host would have any effect on the size of the cysts of an infection. The investigation of this question is accompanied, however, with obvious difficulties. The existence of two strains, the 'small' ( $7.7\mu$ ) strain and the 'ordinary' ( $12.6\mu$ ) strain, is considered to be established.

*Size strains in E. coli cysts*

In Table VIII are given in ascending order of size the average diameters of all the *E. coli* infections of which fifty or more cysts were measured.

TABLE VIII.

No. of infection	Number of cysts measured	Average diameter ( $\mu$ )
1	51	15.6
2	50	15.8
3	50	16.3
4	50	16.4
5	100	17.0
6	52	17.4
7	51	17.5
8	53	17.6
9	190	18.6
10	50	18.6
11	50	18.8

Just as in the case of *E. histolytica* the averages are fairly evenly distributed between the two extremes. There is a considerable interval ( $1\mu$ ) between Infection 8 and Infection 9, which may indicate that the species is split up into at least two size strains, but nothing definite can be said until more infections and larger samples of these

FIG. 4. Two infections of *E. histolytica* 'ordinary' strain  
100 cysts and 140 cysts.

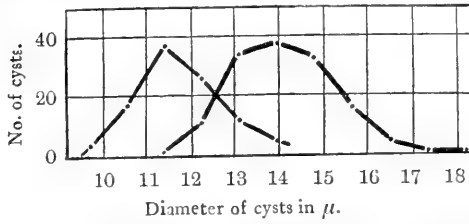


FIG. 5. The two infections of Fig. 4 in one curve. 240 cysts.

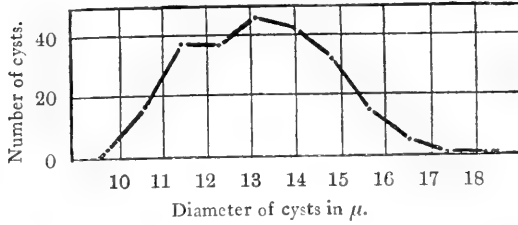


FIG. 6. 300 cysts from all the cases who have never left England.

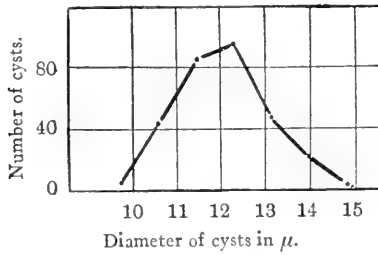


FIG. 7. Three infections (244 cysts) of large cysts of *E. histolytica*.

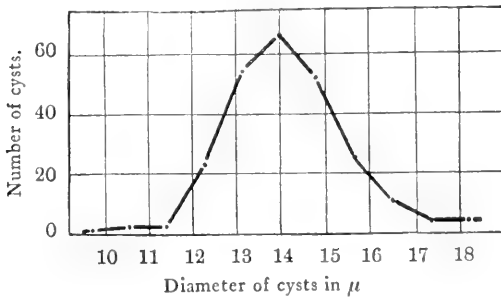
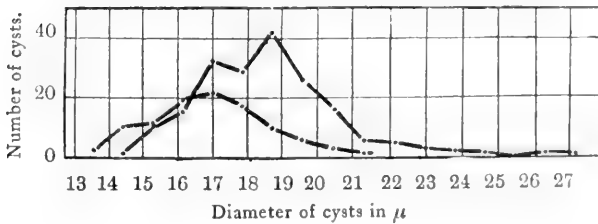


FIG. 8. Two infections of *E. coli*. 100 cysts and 190 cysts.



have been measured. Table IX gives the variation from one day to another in the size of the cysts of a few infections.

TABLE IX.

No. of infection	Date of examination	Number of cysts measured	Average diameter ( $\mu$ )
9	10.7.17	20	18.6
	11.7.17	65	18.6
	25.7.17	24	19.3
	26.7.17	21	18.2
	30.7.17	20	18.8
	1.8.17	40	18.2
5	14.11.17	50	16.8
	29.11.17	25	16.6
	24.1.18	25	17.7
6	17.9.17	28	16.8
	18.9.17	24	18.1
8	26.11.17	21	17.1
	27.11.17	32	17.9

The evidence upon the important question as to whether change in cyst size occurs from one day to another is insufficient. The samples measured are usually too small. In Infection 8 the agreement is fairly close between one day and another. In Infections 5, 6 and 9 there are differences of over  $1\mu$  between the extremes of the average measurements. In Infection 9, however, the extremes are connected by averages intermediate between them, so that the whole infection remains fairly uniform. Further measurements of large samples are required before it can be stated whether variations do or do not occur outside the limits of error of sampling.

In fig. 8, p. 57, the measurements for the two largest samples, one hundred from Infection 5 and one hundred and ninety from Infection 9, are given in the form of curves. The curves represent the following figures:—

Scale-divisions		...	...	8.0	8.5	9.0	9.5	10.0	10.5	11.0
Number of cysts	Infection 9	...	...	...	1	10	15	32	28	42
	Infection 5	...	...	2	10	11	19	21	17	10

Scale-divisions		...	11.5	12.0	12.5	13.0	13.5	14.0	14.5	15.0	15.5	16.0
Number of cysts	Infection 9	26	16	6	5	3	2	1	0	1	1	
	Infection 5	6	3	1	...	...	...	...	...	...	...	



Taken by themselves these would seem to belong to two distinct strains, but as there are infections apparently intermediate between them in size, the matter cannot be settled without further data. If two, or even three, different size strains of *E. coli* occur, then cases would probably exist having an infection of the pure strains only, while other cases would doubtless show mixtures of two or more of the pure strains. In such a state of things the measurement of samples from a large number of cases would reveal a series of infections ranging pretty evenly between the two extremes of size, and differing from each other by comparatively small amounts, such a series in fact as Table VIII shows. It becomes thus exceedingly difficult to establish the existence of strains which lie so near together in average size as, say,  $1.5\mu$ . Only by measuring large samples of a large number of infections could the matter be settled. It would be very desirable also to settle the question as to the effect of a different host upon the average size of the cysts of an infection. Until these two lines of enquiry have been followed up the question must be left open.

It may be recorded that in one case there appeared to be an effect of emetine bismuth iodine treatment upon the size and shape of the cysts of an *E. coli* infection. Before the treatment fourteen cysts were measured on November 8th, 1917. The average size was  $17\mu$ . The treatment caused a disappearance of *E. coli* cysts from the stools for a period. Their first reappearance in the stools was on November 30th. On this date twenty cysts were measured, and their average size was  $20.4\mu$ . This increase of size is quite outside the usual limits of variation for such samples. Not only were the cysts large, but they were much more irregular in shape. Before the treatment only one cyst out of fourteen was recorded as asymmetrical. Afterwards fourteen out of twenty were recorded as asymmetrical.

### SUMMARY

It will be of interest to summarise the results of the present work in their bearing upon the question of the diagnosis of the cysts of *E. histolytica* and *E. coli*.

#### *The size of the cysts*

It has been shown to be possible, relying upon other characters than that of size for the diagnosis of the species, to obtain two curves

showing the frequency of the various sizes of cysts in the two species. These two curves give information as to the amount of overlapping in size of the cysts of the two species. It is shown that between  $12\mu$  and  $18\mu$  (other authors give  $11\mu$  to  $20\mu$ ) cysts of both species may occur. The present curves show, however, that the extreme sizes are so rare that the probability of their occurrence is very small. It is only between  $13\mu$  and  $15.5\mu$  that any considerable numbers of both species of cysts occur. Consequently, except between these limits, the factor of size may be given considerable weight in the diagnosis.

#### *The shape of the cysts*

*E. histolytica* cysts are somewhat more often distinctly asymmetrical than are *E. coli* cysts. Judged by the same standard of asymmetry, 21 per cent. of *E. histolytica* cysts are asymmetrical, while only 16.5 per cent. of *E. coli* are so.

#### *The number of nuclei*

It has been shown that the two species differ very much in the comparative frequency of the mature (tetranucleate for *E. histolytica*, 8-nucleate for *E. coli*) cyst in the stools. For *E. coli*, at any rate, it has been proved that the comparative rarity or abundance of cysts in the early stages of nuclear division depends upon the character of the stool, the immature cysts being more frequent in loose stools. Though no similar proof is forthcoming in the case of *E. histolytica*, yet it becomes important to state that the figures obtained refer to infections for the most part from formed and semi-formed stools. In such material mature cysts of *E. histolytica* formed 53 per cent. of all those encountered, while in *E. coli* 87 per cent. of all the cysts were mature. Since the stools were similar for the two species, it is clear that *E. histolytica* cysts more frequently escape to the exterior in the faeces while in the early stages of nuclear division. Problems of diagnosis are much simplified by this difference between the two species, for the rule that all cysts with more than four nuclei are diagnosed as *E. coli* at once settles the diagnosis of approximately 90 per cent. of all the cysts of *E. coli* encountered. At the same time, I cannot agree with the statement of Wenyon and O'Connor (1917) that 'the presence of four nuclei in the fully-developed *E. histolytica* cysts is so universal that one can state with

certainty that this is a reliable feature for diagnostic purposes.' It is true that the fully-developed cyst of *E. histolytica* contains four nuclei, but this only helps the diagnosis in so far that cysts with more than four nuclei can be certainly referred to *E. coli*. The presence of four nuclei in a cyst is not, however, in itself a reliable feature for diagnosis, since an *E. coli* cyst obviously may contain four nuclei. Moreover, it has been shown in the present series of observations that only about half of the cysts of *E. histolytica* are in the tetranucleate stage, the remainder being mono- or binucleate. Since *E. coli* cysts may also be mono- or binucleate, a large number of cysts must remain doubtful if regard be paid solely to the number of their nuclei. It can be said, now that the present work has shown that mono- or tetranucleate cysts of *E. coli* are comparatively rare in the stools of dysentery convalescents, that if these numbers of nuclei occur in a cyst, there is a considerable probability that the cyst in question is that of *E. histolytica*. Also if an infection occurs in which anything like half the cysts are tetranucleate, *E. histolytica* must be present. Such considerations, however, cannot be decisive; for instance, an infection such as the one just mentioned, though it must contain *E. histolytica*, may also contain *E. coli*. The fact that I have not encountered a single infection of *E. coli* which did not contain some 8-nucleate cysts is more decisive. It appears from my experience that the 8-nucleate cyst is present in every infection of *E. coli* cysts from similar material to that used in the present work. In spite of the exception taken to the above statement of Wenyon and O'Connor, I completely agree with them in their contention that the cysts of the two species are distinct. Taking all characters into account, I have no doubt that a correct diagnosis can be given in the overwhelming majority of cases. As was stated earlier, the chief difficulty in diagnosis occurs with tetranucleate, and to a less extent with binucleate cysts. Nuclear characters, described previously, usually suffice to distinguish *E. histolytica* from *E. coli* in the mononucleate stage (the great rarity of mononucleate cysts of *E. coli* being also taken into account). The vacuolated binucleate *E. coli* cyst, with its large, deeply-staining vacuole and usually lenticular nuclei, is very characteristic and cannot be mistaken. The non-vacuolated binucleate *E. coli* cyst can usually be diagnosed by the large amount of peripheral chromatin in its nuclei, and also

by its colour and by the uniformity of its cytoplasm. Sometimes, however, a single binucleate cyst is undeterminable. The tetranucleate cyst without chromatoid bodies is the most difficult to diagnose, for the nuclear characters are occasionally not decisive at this stage. The nuclei of a tetranucleate *E. coli* cyst, however, are of larger size both actually and relatively to the cyst than in *E. histolytica*, and the tetranucleate *E. coli* cyst has usually the colour and texture of the cytoplasm characteristic of this species, so that a diagnosis can usually be made. Considering the comparative rarity of tetranucleate *E. coli* cysts, the difficulty in practice is not of great importance. The differences between the tetranucleate cyst of *E. histolytica* and that of *E. coli* are seen in figs. 8 and 14 of the Plate accompanying Matthews' (1918) paper.

#### *The chromatoid bodies*

The chief result of this work as to the chromatoid bodies is to reduce their importance as a character for diagnosis on account of their comparative infrequency. It has been shown that in the average *E. histolytica* infection, as seen in the routine examination of convalescent dysenterics, slightly over half of the samples do not show any cysts containing chromatoid bodies. If a case can be subjected to continued examination, my figures show that cysts containing chromatoid bodies will be found in the vast majority of cases. Since, however, it is usually required, and is certainly desirable, that an absolute diagnosis shall be given on a single examination, the former figures, which show that in half the examinations the diagnosis must be made without the help of chromatoid bodies, are the more relevant. When we consider cysts, rather than infections, we see that only about one-quarter of all the cysts of *E. histolytica* contain chromatoid bodies. Even if all the doubtful cases are included as positive for chromatoid bodies, there still remain two-thirds of the cysts of *E. histolytica* which do not contain chromatoid bodies.

In *E. coli* only 5 to 6 per cent. of all the cysts have chromatoid bodies, though at one time or another about 20 per cent. of the cases with an infection of *E. coli* show cysts containing chromatoid bodies. Though these bodies occur rather rarely in *E. coli* cysts, yet when they do occur they are of great help in diagnosis, being almost always characteristic for the species.

A diagnostic table will now be given adding the results of measurement and enumeration to those given earlier in the paper.

	<i>E. histolytica</i> cysts	<i>E. coli</i> cysts
Size ... ..	5 to 20 $\mu$ . Two size strains exist of average diameter, 7.7 $\mu$ and 12.6 $\mu$ respectively. Of the 'smaller' strain 93 % of the cysts lie between 6 and 9 $\mu$ in diameter. Of the 'ordinary' strain 93 % lie between 10 $\mu$ and 14 $\mu$ and 96 % between 10 $\mu$ and 15 $\mu$ .	12 to 34 $\mu$ : 97 % lie between 13 and 22 $\mu$ in diameter, 84 % lie between 14 and 20 $\mu$ .
Number of nuclei ...	1 to 4: 53 % tetranucleate. 33 % mononucleate.	1 to 16: 87 % 8 nucleate, 89 % with more than 4 nuclei.
Character of nuclei ...	Peripheral chromatin of small granules more or less evenly distributed. Nuclei in consequence less distinctly visible.	Peripheral chromatin of larger unevenly distributed masses. Nuclei, therefore, more distinctly visible.
Cytoplasm ... ..	Colour greenish, typically not uniform in appearance.	Colour paler, greyish, except in the vacuolated binucleates which form about 4 % only of the cyst population. Typically uniform in appearance.
Inclusions ... ..	Chromatoid bodies more frequent, present in $\frac{1}{3}$ of the cysts, but in almost all the infections. In about $\frac{1}{2}$ the examinations all the cysts are without chromatoid bodies. Rod-shaped, with square or rounded ends.  Vacuoles more frequent, one or more in the cyst, usually faintly stained by iodine, with less sharply defined edges.	Chromatoid bodies less frequent, present in about 5 % of the cysts, and 20 % of the infections. In the great majority of the examinations all the cysts are without chromatoid bodies. Irregular in shape, with pointed or splintered ends.  Vacuoles less frequent, generally single in the cyst, usually deeply stained by iodine, and with more sharply defined edges.
Cyst wall ... ..	Thinner ... ..	Thicker.
Shape ... ..	More often asymmetrical ... ..	Less often asymmetrical.

## CONSIDERATION OF THE RESULTS OF OTHER WORKERS

Certain results of previous workers have been quoted in the course of this paper, but it may be useful also to comment on other work on the same lines as the present. Since the rule that all cysts with more than four nuclei belong to *E. coli* has proved to be of

such fundamental importance, it is necessary to say something on the question whether *E. histolytica* cysts ever contain eight nuclei. Kuenen and Swellengrebel (1913) and Swellengrebel and Schiess (1917) have affirmed the existence of 8-nucleate cysts in *E. histolytica*. I fully agree with Mathis and Mercier (1917) and with Dobell and Jepps (1917) in thinking the evidence brought forward by these authors insufficient to establish the existence of such cysts. More recently Brug (1917) has brought forward a case in which the evidence for the existence of a cyst of *E. histolytica* with eight nuclei is somewhat stronger. The cyst in question occurred in an infection in which all the remaining cysts were 1- to 4-nucleate and in which the majority were 4-nucleate. The stools of the patient producing this specimen had been often examined microscopically, and no *E. coli* had ever been seen. The size of the 8-nucleate cyst was  $12\mu$ , and it had a thin wall and small nuclei. The evidence, even in this case, is not complete. Brug unfortunately does not state how many times the stools of this patient were microscopically examined. Dobell (1916) has instanced a case in which an *E. coli* infection was not found until the thirty-seventh examination, and this case was only positive three times in one hundred and seven examinations. Carter, Mackinnon, Matthews and Malins Smith (1917) give a case in which an infection of *E. coli* was not detected until the forty-fifth examination. Since undoubted *E. coli* infections may show themselves as infrequently as in these cases, it becomes no longer surprising that an infection of *E. coli* should show itself very rarely while an accompanying infection of *E. histolytica* might be present much more regularly. It is, therefore, not possible to assert on this account alone that Brug's single 8-nucleate cyst was a cyst of *E. histolytica*. Neither can it be absolutely diagnosed by its size,  $12\mu$ . Though *E. coli* cysts of this size are rare, yet they undoubtedly do exist, and therefore size alone cannot give a certain diagnosis. The thickness of the wall is not in itself a character to which much importance can be attached. It seems, therefore, that though Brug's instance is better founded than previous ones, it is still possible to interpret it as a case in which a very scanty and infrequent infection of *E. coli* accompanied the infection of *E. histolytica*. A case comparable to that given by Brug, but with the *E. coli* infection appearing still

more infrequently, was that of a patient who was examined during the present work and who had an infection of *E. histolytica* which proved very refractory to all kinds of treatment. In consequence his stools were examined a very large number of times. The stools, in fact, were examined on one hundred and sixty-six occasions, on one hundred and twelve of which cysts of *E. histolytica* were present. On the seventy-second and on the one hundred and thirty-eighth examination *E. coli* was recorded. On the second of these occasions the record was based on a single 8-nucleate cyst. On the first occasion not more than two *E. coli* cysts were seen, but no record was made of the number of nuclei. On the ground of the infrequency of the appearance of 8-nucleate cysts in a frequent *E. histolytica* infection, this is a very strong case for the occurrence of an 8-nucleate cyst of *E. histolytica*. But such a consideration is not a reliable basis for diagnosis, and the 8-nucleate cyst was regarded as being undoubtedly *E. coli*. If 8-nucleate cysts of *E. histolytica* occur, they must be so rare as scarcely to affect the question of diagnosis, and certainly their occurrence has not yet been proved.

*Previous records of the extremes of size in cysts of  
E. histolytica and E. coli*

My own records are  $5\mu$  to  $18\mu$  for *E. histolytica* cysts,  $12\mu$  to  $34\mu$  for *E. coli*. They may be compared with the following:—

	<i>E. histolytica</i>	<i>E. coli</i>
Dobell and Jepps (1917) ... ..	5 to 20 $\mu$	11 to 33.5 $\mu$
Kuenen and Swellengrebel (1913) ... ..	11 to 19 $\mu$	13 to 28 $\mu$
Mathis and Mercier (1917b) ... ..	11 to 15 $\mu$	14 to 28 $\mu$
Brug (1917) ... ..	7 to 20 $\mu$	10 to 25 $\mu$
Wenyon and O'Connor (1917) ... ..	6 to 18 $\mu$	13 to 36 $\mu$
Craig (1913) ... ..	7 to 20 $\mu$	...
Woodcock and Penfold (1916) ... ..	7 to 8 and 10.5 to ? $\mu$	..

Besides these records, James (1914) has recorded a case in which the 8-nucleate cysts averaged only  $10\mu$ , and Wenyon (1913) has

recorded 8-nucleate cysts of  $9\mu$  in diameter. These are, however, isolated records, and in neither case is it distinctly stated that the cysts were measured in the fresh state. Apart from these, all the evidence points to  $11\mu$  being the extreme lower limit of size of *E. coli* cysts. Undoubtedly those observers whose lower limit for *E. histolytica* cysts is  $10\mu$  or  $11\mu$  have failed to observe what has been called in this paper the 'small' strain, infections of which have of late constituted about one-quarter to one-third of all the records of *E. histolytica* at the Liverpool School of Tropical Medicine.

*Frequency curves for E. histolytica and E. coli cysts*

Frequency curves have been given by Kuenen and Swellengrebel (1913) and Mathis and Mercier (1917). The curves given by the former, though based on far too few measurements, one hundred cysts only in each species, are in close agreement with the curves given in the present paper. Except for the fact that the 'small' strain of *E. histolytica* has been entirely omitted, their curves take the same general course as my own. With the curves given by Mathis and Mercier (1917) on the other hand, my curves, based on one thousand cysts, show no agreement whatever. The presence of two marked peaks in their curve for *E. histolytica* and three peaks in their curve for *E. coli*, with very few records between the peaks, is quite inexplicable to me. I am convinced from the measurement of much larger numbers than theirs that the dimensions of both species of cysts increase by infinitely small stages from one extreme to the other, and that, though the curves may not be perfectly smooth, there are no marked breaks in the series. I am, therefore, also unable to support their theory (Mathis and Mercier 1917c) of the occurrence in *E. histolytica* of 'kystes gamogoniques' of two types, microcysts and macrocysts, and in *E. coli* of 'kystes gamogoniques' or 'sexués' and 'kystes schizogoniques' or 'asexués,' the former kind being divided as in *E. histolytica* into microcysts and macrocysts. This theory is so closely associated with their peculiar frequency curves for the sizes of the two species of cysts and depends so much upon those curves for evidence, that the theory cannot very well stand unless the curves are accurate. Whatever may be the truth upon this latter point, it is quite clear that the numbers measured by these authors were far too few.



*The possibility of distinguishing the two species of cysts*

It is clear that all the work of the present paper implies a belief that *E. histolytica* and *E. coli* are separate species which can be distinguished from each other in the encysted stage.

In this belief the writer is supported by Wenyon and O'Connor (1917), Dobell and Jepps (1917), Mathis and Mercier (1917), as well as by the majority of less recent writers. Gauducheau (1915) has, however, stated the opposite view on what appear to me quite insufficient grounds. He acknowledges the reality of the presence in certain stools in Tonkin of two types of cysts, the larger with eight nuclei and the smaller with four nuclei. It appears to me that the separation into these two types (species) is possible, in spite of the fact that any particular diagnostic criterion may occasionally break down. More recently Knowles and Cole (1917) have enunciated the view that *E. coli* and *E. histolytica* are one species, and have even suggested for this species the name *E. coli communis*. Their chief evidence for this conclusion is that when they separated the species according to 'text-book teaching as to differentiation between amoebic species and after a full and careful examination of all accessible information with regard to each patient,' they could find no clear differential characters of any kind which would serve to separate the one species from the other. This conclusion is supported by several curves and tables showing the results of large numbers of careful measurements and observations. These all appear to support the deduction that neither in size, number of nuclei, character of nuclei nor pathogenicity do the two species show any clear differences. Since these curves and tables are entirely opposed to my own conclusions, it is desirable to put forward an explanation which would reconcile the two sets of measurements. I suggest as a tentative explanation of the work of Knowles and Cole a modification of a criticism which suggested itself to the authors themselves, namely, that the great majority of the cysts they measured were cysts of *E. coli*, and that only a small proportion were really *E. histolytica*. Probably only the infections which they separated out as *E. minuta* were really *E. histolytica*. The hypothesis that the stools in general, and particularly the series used for the measurements, contained fewer *E. histolytica* infections and more *E. coli* infections than the authors recorded would explain the difference between their results and those

of other workers. It would bring the general results of their examinations (see their Table III) more into line with what is usually found as to the relative frequency of *E. coli* and *E. histolytica* infections. It would explain the paucity of tetranucleate cysts and their large average size ( $15.5\mu$ , see their Table IV), which might well be the average size of a mixed lot of cysts of the two species in which *E. coli* predominated. If, too, the real *E. histolytica* cysts were excluded from the figures on which Charts C1, C2, and C3 were based, by being separated out under the name *E. minuta*, then one would expect the remaining cysts, however divided artificially into two species, to give almost coincident graphs such as are presented in these charts. The great rarity of chromatoid bodies in the cysts also points in the direction of the cysts being prevailingly cysts of *E. coli*. The fact that many of the cases were those of acute or convalescent dysenterics does not dispose of this criticism, for Wenyon and O'Connor (1917) record that in nine hundred and sixty-one patients admitted to hospital in Egypt for dysentery, diarrhoea and related intestinal disorders, a single examination revealed the cysts of *E. histolytica* in only 2.2 per cent. of the cases. Unfortunately the authors nowhere state definitely what morphological criteria they relied upon in making diagnoses. The statements in the text-books are so conflicting and unreliable that one cannot gather their criteria from the recorded fact that they followed those given in the text-books. Until the authors state clearly on what morphological grounds—entirely apart from the dysenteric history of the patient, which ought to carry no weight whatever, since bacillary dysentery is so prevalent—their diagnoses were made, the simplest hypothesis which will bring their results into line with those of other workers is to suppose that the great majority, though not all, of their cysts were those of *E. coli*.\*

Brug (1917) has considered the question of the differential diagnosis of the two species, and has concluded that there is no one single character which taken alone is decisive in diagnosis, but that by the totality of characters shown by a number of cysts one can arrive at a definite diagnosis. This is substantially the position taken up in the present work, though, as already stated, I do not

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\* A paper by Brug (1918) has appeared since the above was written, making substantially the same criticism of the work of Knowles and Cole.

think Brug's instance to the contrary is sufficiently well founded to invalidate the rule that cysts with more than four nuclei are those of *E. coli*. Undoubtedly, as Brug states in opposition to Mathis and Mercier, and as is also stated by Dobell and Jepps (1917) and Chatton (1917), the cysts of both species contain chromatoid bodies. I disagree with Brug, however, in thinking that the form of these is similar in the two species of cysts. Rod-shaped chromatoid bodies typical of *E. histolytica* are at any rate exceedingly rare in *E. coli*, and when they occur are usually narrower and more needle-like than in *E. histolytica*.

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# STUDIES IN THE TREATMENT OF MALARIA

## XIII.—ORAL ADMINISTRATION OF QUININE SULPHATE GRAINS 90 ON TWO CONSECUTIVE DAYS ONLY, IN SIMPLE TERTIAN MALARIA

### [SECOND SERIES]

BY

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*(Received for publication 1 June, 1918)*

In a previous paper (1918) we recorded the results of administration of quinine sulphate in solution grains 90 on each of two consecutive days to a series of seventy-six cases of simple tertian malaria. Sixty-two per cent. of the cases treated did not relapse within an observation period of sixty days or longer (in four cases the observation period was only fifty-three, fifty-three, fifty-four and fifty-eight days respectively). In the present paper we record the results of the same treatment in a second series of eighty-nine cases.

A summary of the results is given in Table II, which also contains

the following additional information:—Place of infection, and interval in months between present treatment and (a) first admission to a hospital for malaria, (b) leaving infected area, (c) arrival in England.

In all cases quinine sulphate in solution was given orally either in three doses of grains 30, or six doses of grains 15 on each of two consecutive days.

Blood examinations were made daily in all the cases.

Parasites disappeared from the blood as a rule in one to two days, in all cases within five days. The temperature fell to normal either on the day of the first dose or within one to three days.

*Relapses.* In eighty-four of eighty-nine cases a parasitic relapse occurred in twelve to fifty-three days, average eighteen days. In three cases there was no parasitic relapse within an observation period of sixty days. Case 761 was discharged on the twenty-seventh day, and Case 811 on the fortieth day. In sixty-four cases true febrile relapses occurred in thirteen to fifty-four days. Two cases (809 and 813) relapsed parasitically on the sixteenth and thirty-ninth days; parasites were not found again and there was no febrile relapse up to the eighty-fifth and seventy-third days respectively.

*Tolerance of treatment.* A number of cases presented symptoms of quinine poisoning, e.g. deafness, giddiness, vomiting, tremors, dimness of vision. One case (750) became temporarily blind. In all cases unfavourable symptoms disappeared within two to three days.

## SUMMARY

In this series of eighty-nine cases treated with quinine sulphate in solution grains 90 on each of two consecutive days, at least eighty-four, i.e. 94 per cent., relapsed. As two cases were observed for less than sixty days the possible maximum number of relapses within an observation period of sixty days is eighty-six, i.e. 97 per cent.

A comparison of the results obtained in this series of observations with those obtained with the same treatment in the previous series (1918) is given in the following table.

TABLE I.

Comparison of results of oral administration of quinine sulphate grains 90 on two consecutive days only in Series I and Series II.

	Series I		Series II	
Number of cases treated ... ..	76		89	
	Minimum	Maximum	Minimum	Maximum
Number of cases which relapsed* ...	29	33	84	86
Percentage of cases which relapsed ...	38 %	43 %	94 %	97 %

\* As explained in Papers VII and VIII (1918), the minimum figure refers to the relapses actually observed, while the maximum is the sum of these and of such cases as left hospital before the completion of the 60 days' observation period.

The explanation of the remarkable discrepancy between these two results we propose to discuss in a future paper.

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TABLE II.

Summary of results of oral administration of quinine sulphate grains 90 on each of two consecutive days.

\* E.A. = East Africa. F. = France. I. = India. M. = Mesopotamia. S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Parasitic relapse occurred in — days after first dose	Febrile relapse (above 100° F.) occurred in — days after first dose	Observation period in cases in which did not relapse	Remarks
731	E.A.	10	4	1	31.3.18	2	1	16	14	...	
732	E.A.	7	4	1	11.4.18	1	2	17	16	...	
733	E.A.	5	4	1	12.4.18	Same day	2	22	19	...	
734	S.	7	5	4	22.3.18	1	3	15	20	...	
735	E.A.	10	2	0	29.3.18	1	2	13	...	...	Quinine orally gr. 45 on 14th day
736	E.A.	19	3	1	12.4.18	Same day	2	16	22	...	
737	S.	19	2	2	22.3.18	1	2	18	...	...	Quinine orally gr. 45 on 21st day. Crescents on 17th and 18th days
738	E.A.	6	1	0	29.3.18	1	1	15	18	...	
739	S.	7	2	2	24.3.18	1	3	14	13	...	
740	S.	7	3	3	10.4.18	3	2	13	15	...	
741	E.A.	9	3	1	12.4.18	1	2	17	...	...	Quinine orally gr. 15 on 18th day
742	M.	10	8	4	9.3.18	1	1	17	18	...	
743	M.	9	8	4	29.3.18	1	2	42	...	...	Quinine orally gr. 15 on 42nd day
744	S.	8	2	1	29.3.18	Apyrexia	1	12	13	...	
745	E.A.	4	2	0	29.3.18	1	1	13	16	...	
746	S.	6	2	1	4.4.18	Apyrexia	1	13	15	...	
747	E.A.	21	6	1	12.4.18	Apyrexia	1	26	23	...	



748	S.	9	3	1	17.1.18	1	2	14	16	...	Quinine orally gr. 90 on 16th day
749	S.	10	4	2	4.2.18	1	2	16	18	...	
750	S.	11	4	2	25.2.18	1	2	12	...	...	
751	S.	12	5	3	13.3.18	Apyrexia	1	14	17	...	
752	E.A.	16	3	1	11.4.18	Same day	1	16	23	...	
753	E.A.	24	4	1	3.4.18	Apyrexia	1	...	...	63	
754	E.A.	13	9	3	31.3.18	Apyrexia	Same day	...	...	72	
755	E.A.	10	4	1	12.4.18	Apyrexia	1	27	...	...	Quinine orally gr. 15 on 28th day
756	E.A.	6	5	1	4.4.18	1	2	18	19	...	
757	E.A.	6	4	1	12.4.18	Apyrexia	1	16	18	...	
758	S.	21	2	1	24.3.18	1	2	13	18	...	
759	E.A.	9	3	0	29.3.18	Same day	1	14	17	...	
760	E.A.	8	5	4	29.3.18	2	1	20	20	...	
761	I.	...	...	...	12.4.18	Apyrexia	1	...	...	27	Quinine orally gr. 15 on 25th day
762	E.A.	9	3	1	5.4.18	1	1	22	...	...	Quinine orally gr. 45 on 14th day
763	E.A.	9	2	1	5.4.18	Same day	1	13	...	...	
764	E.A.	12	1	0	29.3.18	Apyrexia	1	13	16	...	
765	S.	8	3	2	4.4.18	Same day	3	22	...	...	Quinine orally gr. 15 on 23rd day
766	E.A.	5	3	1	5.4.18	Same day	2	14	...	...	Quinine orally gr. 45 on 15th day
767	E.A.	9	3	1	31.3.18	Same day	1	14	17	...	
768	S.	18	2	1	24.3.18	Same day	2	15	19	...	
769	E.A.	7	3	0	12.4.18	Same day	1	53	54	...	
770	E.A.	7	1	0	31.3.18	Same day	1	19	20	...	
771	E.A.	5	2	0	31.3.18	1	2	25	...	...	Quinine orally gr. 45 on 26th day
772	S.	23	2	1	9.4.18	Same day	1	15	14	...	
773	S.	10	2	0	12.4.18	Apyrexia	1	15	17	...	
774	E.A.	21	1	0	24.3.18	Apyrexia	1	17	...	...	Quinine orally gr. 45 on 19th day
775	S.	8	2	2	22.3.18	Apyrexia	1	12	16	...	

TABLE II—continued.

Summary of results of oral administration of quinine sulphate grains 90 on each of two consecutive days.

\* E.A. = East Africa. F. = France. I. = India. M. = Mesopotamia. S. = Salonica.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Parasitic relapse occurred in — days after first dose	Febrile relapse (above 100° F.) occurred in — days after first dose	Observation period in cases which did not relapse	Remarks
776	S.	9	3	3	11.4.18	1	1	14	...	...	Quinine orally gr. 45 on 15th day
777	E.A.	6	3	0	31.3.18	Same day	2	13	16	...	...
778	E.A.	8	3	1	31.3.18	1	2	14	...	...	Quinine orally gr. 45 on 16th day
779	E.A.	7	3	1	9.4.18	1	2	16	16	...	...
780	E.A.	23	6	5	17.1.18	Apyrexia	Same day	15	18	...	...
781	E.A.	24	7	6	5.2.18	1	1	22	...	...	Quinine orally gr. 90 on 25th day
782	E.A.	25	8	7	2.3.18	Apyrexia	1	15	16	...	...
783	E.A.	25	8	7	19.3.18	Same day	1	20	...	...	Quinine orally gr. 45 on 24th day
784	E.A.	8	3	3	11.4.18	Same day	2	14	...	...	Quinine orally gr. 45 on 15th day
785	S.	17	...	...	16.3.18	1	3	15	15	...	...
786	S.	15	...	...	20.3.18	Same day	1	16	16	...	...
787	S.	17	...	...	26.2.18	1	2	21	22	...	...
788	S.	18	...	...	22.3.18	1	2	20	21	...	...
789	E.A.	11	...	...	20.2.18	Apyrexia	1	17	19	...	...
790	E.A.	12	...	...	12.3.18	2	2	26	29	...	104° on 5th, 102° on 6th days
791	S.	18	3	2	30.3.18	3	2	38	38	...	...
792	E.A.	10	...	...	3.4.18	1	4	14	16	...	...





## STRONGYLIDÆ IN HORSES

### IV. *GYALOCEPHALUS CAPITATUS*, Looss.

BY

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AND

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(Received for publication 15 April, 1918)

This species was described by Looss in 1900. A year later (1901) he amplified his earlier description, although his search for further material had been unsuccessful. As Looss had at his disposal but a single pair of copulating worms, which he had found in the colon of a mule in Egypt, his description is in some respects inadequate. So far as we are aware, no other account of this worm has been published.

The worm has been found by us in small numbers in five horses, and we propose to describe it in detail.

**SIZE AND SHAPE.** A small species which could at once be distinguished with the naked eye from members of the GENUS *Cylicostomum*, with which it was always associated, by the fact that it had a black and white appearance, the coils of the gut standing out clearly on account of their dark contents. One male and nine females were measured. The male was 7 mm. in length, and the females varied from 8.5 to 10.5 mm., average 9.2 mm.; the greatest breadth was, in the male, 156 $\mu$ , and averaged in the females 200 $\mu$ .

**HEAD.** The head is separated from the body by a well-marked neck (fig. 1).

*Mouth collar.* Sharply marked off from the rest of the skin by a deep constriction. The mouth is circular in transverse section.

*Head papillae.* Submedian, fairly stout conical projections reaching as far anteriorly as the external leaf crown; lateral, projecting somewhat beyond the mouth collar.

*Mouth capsule.* Circular in transverse section. It is a highly complicated structure, more closely resembling the state of affairs seen in *Tridentophorus* than that in *Cylicostomum*. It consists of two portions, firstly an extra-oesophageal part, the true buccal

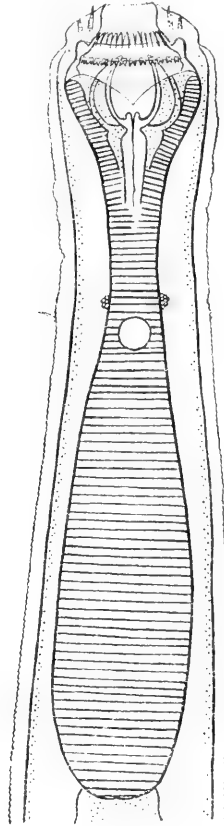


FIG. 1. *Gyaloccephalus capitatus*, Looss.

Anterior extremity, ventral view,  $\times 90$ .

capsule comparable with that occurring in the GENUS *Cylicostomum*, and secondly an intra-oesophageal portion formed by the chitinisation of the oesophageal funnel. The anatomy of the buccal capsule (especially of the intra-oesophageal portion) is so complicated that it can hardly be understood without the aid of transverse and longitudinal sections. Diagrams of transverse sections through different levels are given in fig. 4. *a-f*, and of a longitudinal section in fig. 5.

The walls of the extra-oesophageal portion of the buccal capsule consist anteriorly of a thick chitinous ring which becomes thinner posteriorly and extends backwards over the anterior portion of the oesophageal funnel as three delicate triangular prolongations,

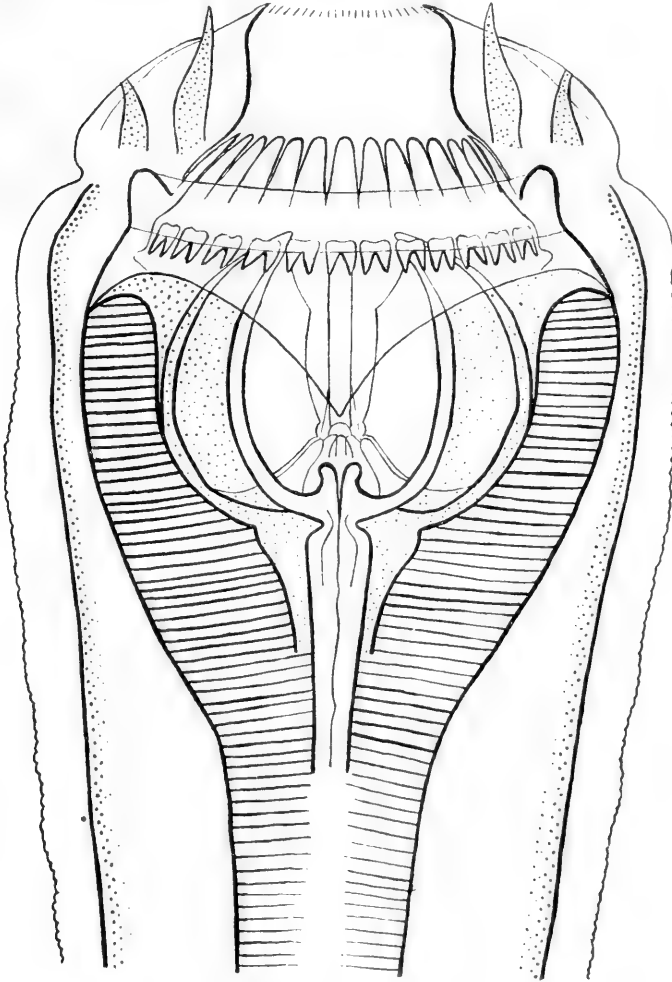


FIG. 2. *Gyaloecephalus capitatus*, Looss.

Head, ventral view,  $\times 360$ .

the apices of which coincide, not with the median lines of the three divisions of the oesophagus as stated by Looss, but with the points of contact of these three divisions (figs. 2 and 3).

The intra-oesophageal part is a hemispherical cavity, into which project from the wall three wedge-shaped septa (*vide* fig. 4. c).

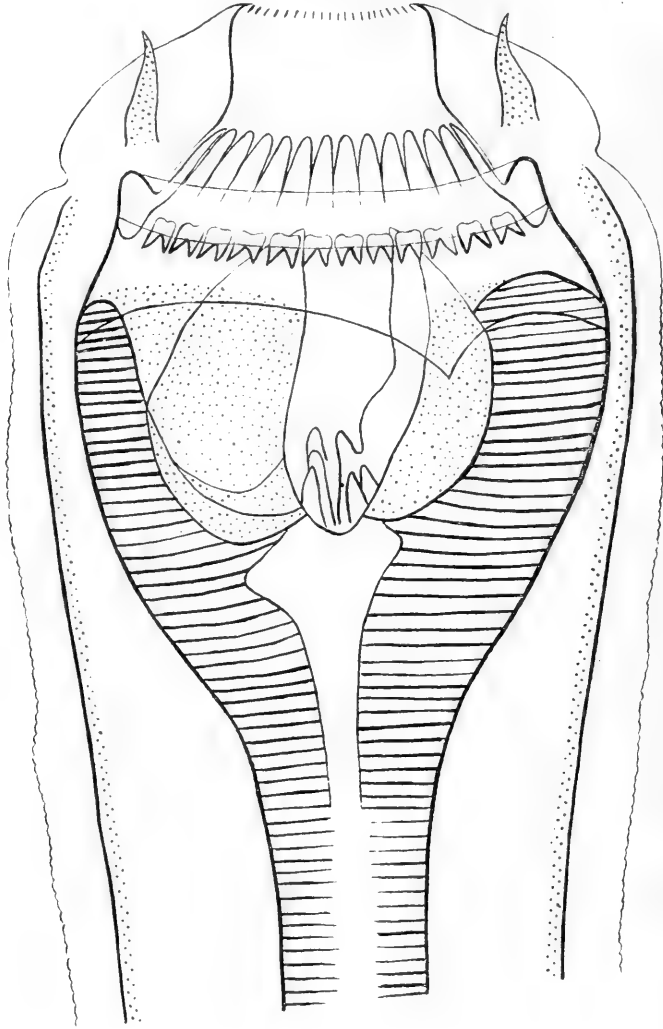


FIG. 3. *Gyaloccephalus capitatus*, Looss.

Head, lateral view,  $\times 360$ .

These wedges represent the continuation upwards of the three oesophageal segments. Each process extends anteriorly to about the level of the posterior margin of the true buccal capsule and there



terminates as a tooth (fig. 4. *b* and fig. 5). At the base of the chitinised oesophageal funnel are three pairs of chitinised ridges forming the edges of the triradiate cavity of the oesophagus (fig. 4. *e*.) These ridges are crescentic in form; following the base of the oesophageal funnel externally they are lost in the wall of the cavity, but internally they project anteriorly as six pointed teeth (fig. 4. *d* and fig. 5).

The antero-posterior diameter of the mouth capsule, measured from the anterior opening of the true buccal capsule to the base of the chitinised oesophageal funnel, was in the male  $108\mu$ , and in five females it varied from  $123\mu$  to  $132\mu$ , average  $128\mu$ ; the lateral diameter at the anterior opening of the true buccal capsule was in the male  $105\mu$ ; in the females it varied from  $123\mu$  to  $136\mu$ , average  $127\mu$ . The ratio of the lateral diameter of the anterior opening of the mouth capsule to the antero-posterior diameter is 1 to 1.

*Dorsal oesophageal gutter.* There is no dorsal oesophageal gutter.

*Leaf Crowns.* The external leaf crown consists of numerous minute slender and pointed elements arising from the mouth collar. The internal leaf crown consists of thirty-two large and stout elements originating from the inner surface of the true buccal capsule. Posteriorly each element terminates in two root-like processes, giving rise to the 'cogwheel' or 'battlement' appearance referred to by Looss (figs. 2 and 3 and fig. 4. *b*).

**OESOPHAGUS.** The most striking character of the genus is the peculiar formation of the anterior end of the oesophagus. It dilates into a large cup-shaped cavity lined by chitin, and armed with teeth in the manner already described. So marked is this dilation that the anterior end of the oesophagus almost completely fills the worm. Posterior to the dilation the oesophagus becomes very narrow, while immediately behind the nerve ring it again enlarges. The whole oesophagus resembles in shape an *Indian club*, the swollen anterior portion representing the handle of the club (fig. 1).

The length measured from the anterior extremity of the cup-like dilation to the posterior end was in the male  $882\mu$ ; in five females the length varied from  $926\mu$  to  $1,026\mu$ , average  $982\mu$ ; the greatest breadth of the posterior expansion was in the male  $156\mu$ , the

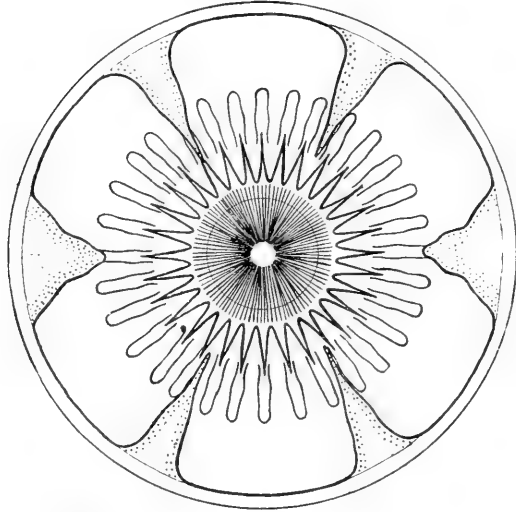
FIG. 4 a-f. *Gyalocephalus capitatus*, Looss.Transverse sections through the anterior extremity,  $\times 360$ .

FIG. 4a. Section through the anterior part of the true buccal capsule showing the external and internal leaf crowns.

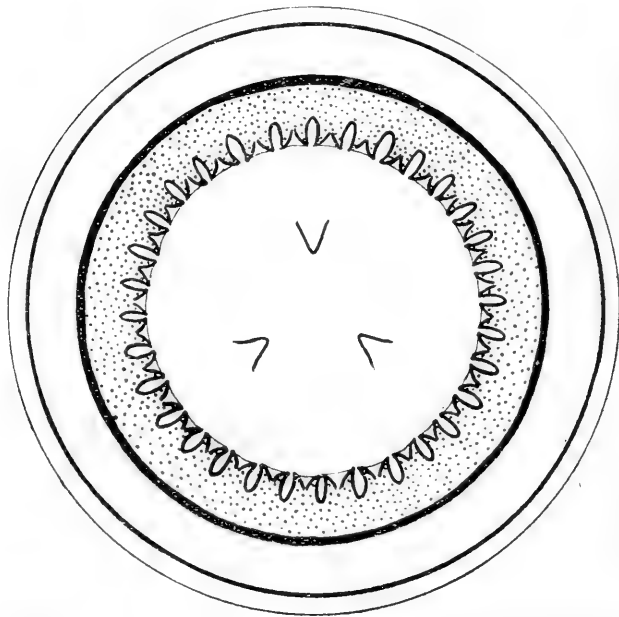


FIG. 4b. Section through the posterior part of the true buccal capsule at the level of the roots of the posterior leaf crown, showing the tooth-like anterior extremities of the three septa.

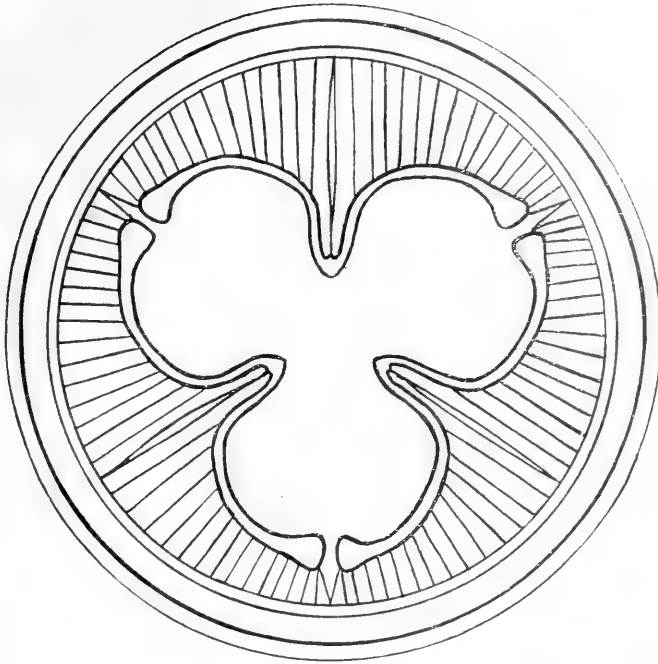


FIG. 4c. Section through the anterior part of the intra-oesophageal portion of the mouth capsule, showing the three septa.

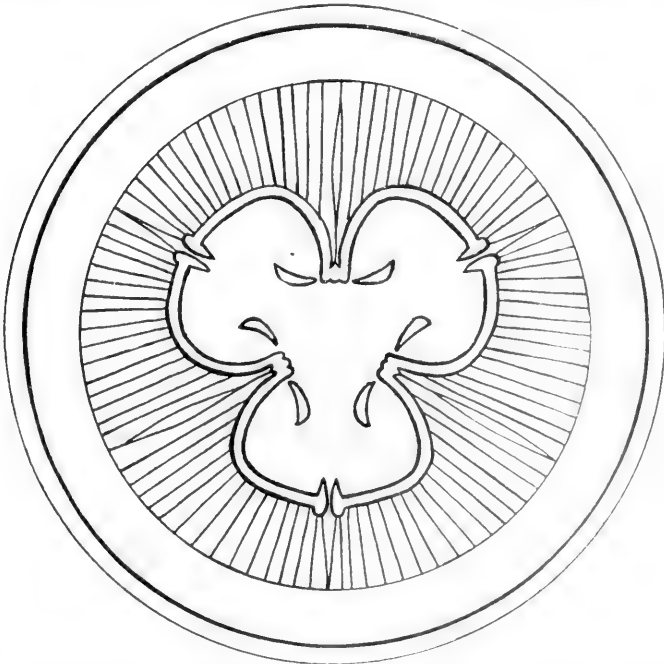


FIG. 4d. Section through the lower part of the intra-oesophageal portion of the mouth capsule, showing the tooth-like terminations of the three pairs of chitinated ridges which guard the entrance to the triradiate oesophagus.

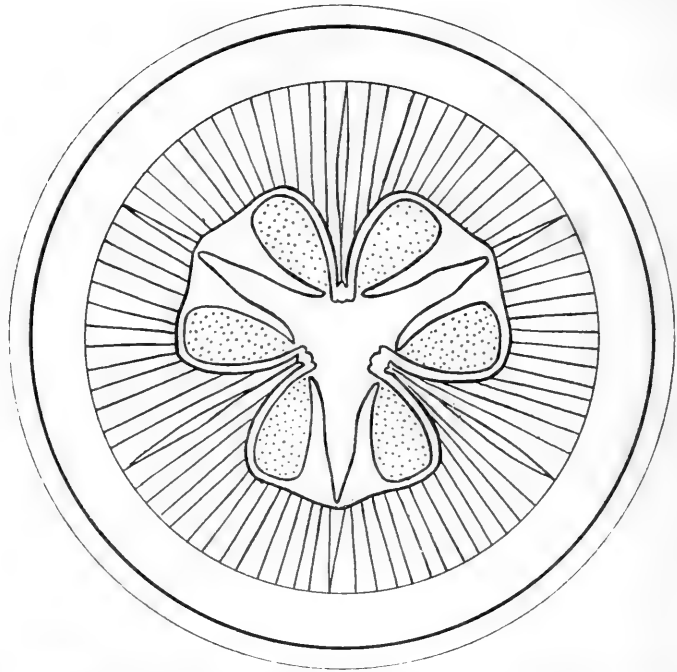


FIG 4e. Section through the base of the intra-oesophageal portion of the mouth capsule, showing the three pairs of chitinated ridges which guard the entrance to the triradiate oesophagus.

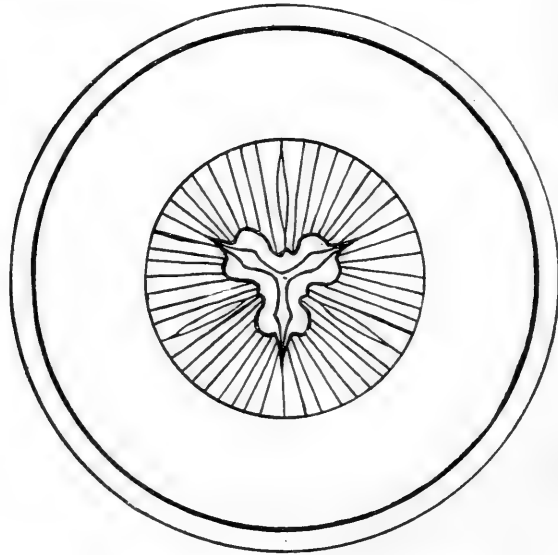


FIG. 4f. Section through the narrow neck of the oesophagus, showing the triradiate cavity.

average greatest breadth in the females was  $200\mu$ . The ratio of average greatest breadth to average length was in the male 1 to 5.6, and in the female 1 to 4.9; and the ratio of the length of the oesophagus to that of the worm was in the male 1 to 8, and in the female 1 to 9.

**EXCRETORY BLADDER.** Lies just behind the nerve ring over the narrow portion of the oesophagus. The distance of its posterior margin from the posterior extremity of the oesophagus varied in six worms from  $557\mu$  to  $664\mu$ , average  $594\mu$ .

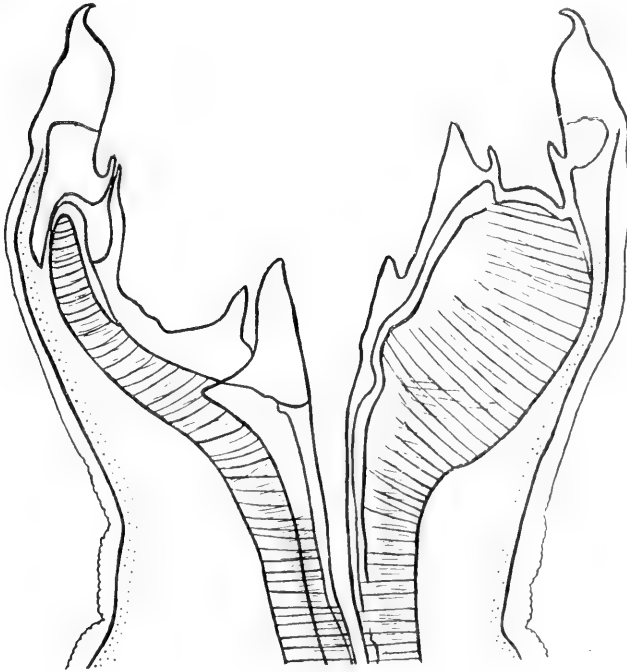


FIG. 5. *Gyaloecephalus capitatus*, Looss.  
Longitudinal section through the head,  $\times 360$ .

**CERVICAL PAPILLAE.** These lie at the level of the excretory bladder.

**POSTERIOR EXTREMITY OF MALE.** The body tapers gradually to the bursa. The dorsal lobe of the bursa is triangular in shape, being more than a semicircle; the lateral lobes are distinctly marked off from the dorsal lobe and are voluminous, embracing the cone ventrally (fig. 6).

The anterior, antero-external and median rays all arise from a

Fig. 6

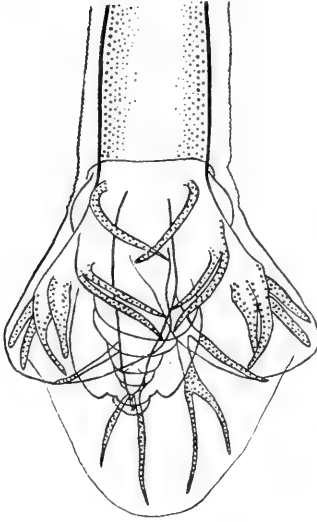


Fig. 7

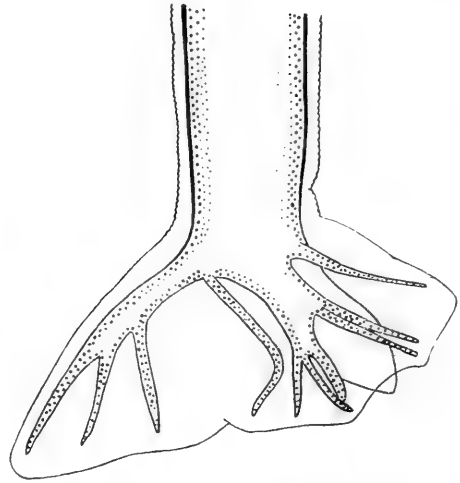


Fig. 8

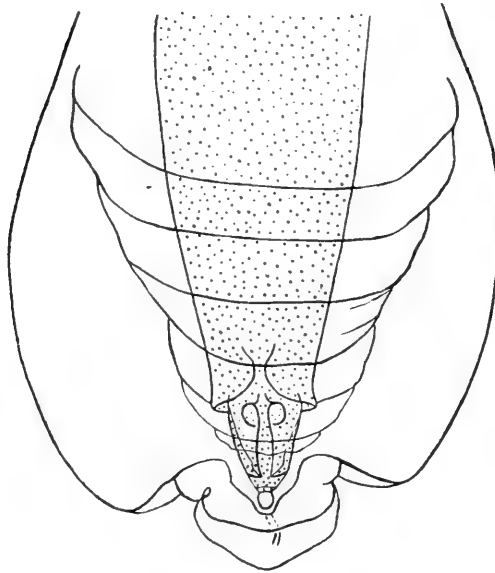
FIGS. 6-8. *Gyalocephalus capitatus*, Looss.

FIG. 6: Posterior extremity of male, ventral view,  $\times 90$ . FIG. 7: Posterior extremity of male, lateral view,  $\times 90$ . FIG. 8: Genital cone and appendages, ventral view,  $\times 360$ .

common trunk. The anterior ray is cleft to its point of origin from the common trunk. The antero-external arises just before the point of bifurcation of the median ray. The postero-external arises at the root of the dorsal ray, it runs at first parallel with the median ray and then bends dorsally. The dorsal ray bifurcates after a short course, and each main branch gives off two lateral sub-branches. The pre-bursal papillae are strikingly long, and are in this worm true rays in that they support the anterior portions of the lateral lobes of the bursa which, as mentioned above, are very voluminous completely embracing the genital cone ventrally (figs. 6 and 7).

The length of the main trunks of the posterior ray, from the tip to the point of origin of the postero-external rays, was  $363\mu$ . The ratio of the length of the main trunks of the posterior ray to the length of the male worm is 1 to 19.

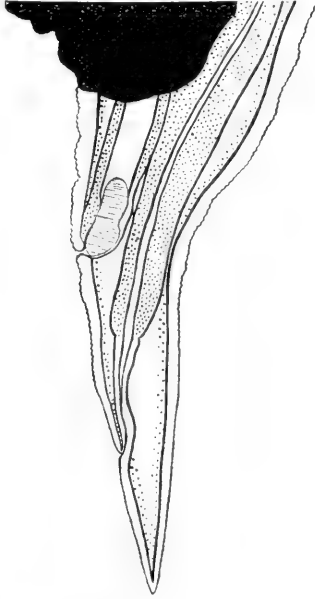


FIG. 9. *Gyaloccephalus capitatus*, Looss.

Posterior extremity of female, lateral view,  $\times 90$ .

*Genital cone.* This structure is prominent, it runs obliquely posteriorly and ventrally from the end of the body and reaches as far as the free margin of the lateral lobes of the bursa. The dermal collar is fairly well developed ventrally, but only slightly so dorsally. There is a remarkable cuticular expansion on each side of the genital cone, extending from its base to the tip (fig. 8).

*Spicules.* We were unable to determine the character of the spicules in the single specimen available.

POSTERIOR EXTREMITY OF FEMALE. The end of the body is straight and tapers slightly to the tail. The tail, which is slightly demarcated from the body, is straight, very long and slender (fig. 9). In five worms the distance between the anus and the vulva varied from  $301\mu$  to  $414\mu$ , average  $369\mu$ , and the distance measured straight along the middle of the tail, from the tip to a line drawn horizontally through the anus, varied from  $203\mu$  to  $298\mu$ , average  $244\mu$ .

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## STRONGYLIDÆ IN HORSES

### V. *GYALOCEPHALUS EQUI*, sp. n.

BY

WARRINGTON YORKE

AND

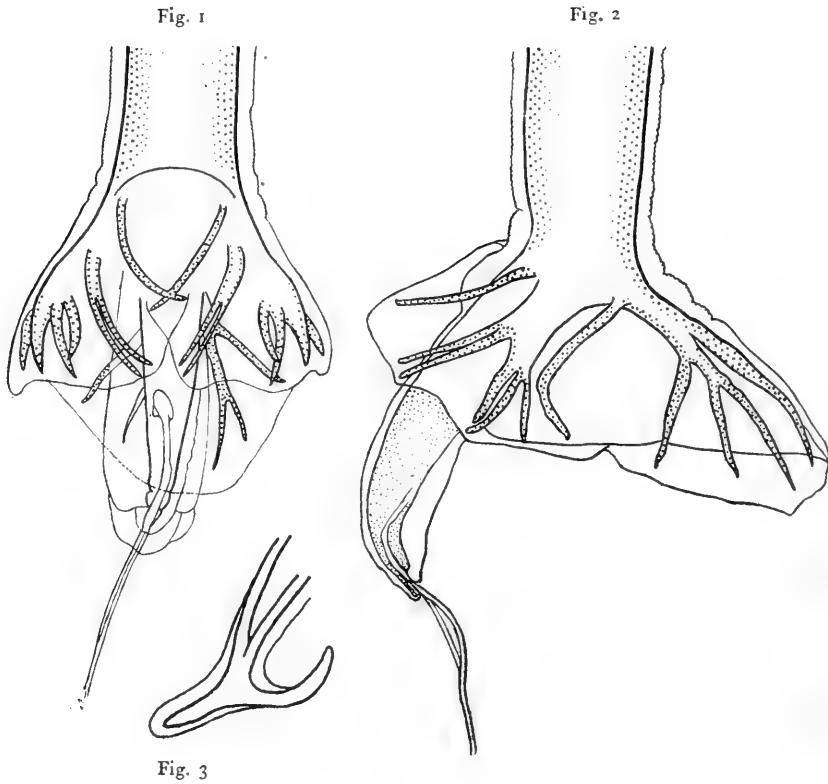
J. W. S. MACFIE

(Received for publication 15 April, 1918)

This worm was found by us in small numbers in three horses. The male can at a glance be distinguished from *Gyalocephalus capitatus* on account of the enormous length of the genital cone. This structure in *Gyalocephalus capitatus* extends only as far as the free margin of the lateral lobes of the bursa, but in this worm it protrudes far beyond the bursa and is about twice as long as in the former species (figs. 1 and 2).

We have been unable to discover any other differences between the males of this worm and those of *Gyalocephalus capitatus*, and the females found *in coitu* with males of this worm were in all respects identical with those of *Gyalocephalus capitatus*. The size of the worm, the structure of the mouth capsule, and the ratios of the length of the oesophagus and of the posterior ray to that of the whole worm are the same as in *Gyalocephalus capitatus*.

We have decided to regard this worm as a new species—*Gyalocephalus equi*—although the sole differential character is the great length of its genital cone. Whether this character is really of specific importance, or whether it is variable in the same species, we do not know. Possibly the cone may be protrusible and retractile, but we must point out that there is no evidence that such is the case in allied genera.



FIGS 1-3. *Gyalocephalus equi*, sp. n.

Fig 1: Posterior extremity of male, ventral view,  $\times 90$ . Fig. 2: Posterior extremity of male, lateral view,  $\times 90$ . Fig. 3: End of spicule,  $\times 1360$ .

# POLYPNEUSTIC LOBES IN THE LARVAE OF TSETSE-FLIES (*GLOSSINA*) AND FOREST-FLIES (*HIPPOBOSCIDAE*)

BY

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Having occasion recently to determine the exact specific differences in the larvae of certain species of tsetse-flies, I discovered to my great joy that the innumerable 'papillae' which form the sculpturing on the exterior of the prominent lobes, at the anal extremity of the body, were respiratory openings, and evidently function as such during the intra-uterine life of the larva. In other words, each so-called 'papilla' represents a separate and distinct stigma, whose tubular continuations are connected with large tracheal trunks in the interior of the lobes. These compound stigmata appear as 'air-holes' of the simplest type, and when seen in optical section, under a low magnification ( $\times 100$ ), their presence gives the integument the appearance, in miniature, of the 'rose' of a florist's watering-can. The ramifications of all the tracheal trunks which almost fill the interior of the lobes have not, owing to their complex nature, been completely traced to the main tracheal system, but there can, I think, be little doubt that they are all connected with the main pair of stigmata (posterior spiracles) which lie in the deep cup-shaped cavity or pit *between* the polypneustic lobes. This remarkable development of the respiratory system in the final larval stage can be seen only in those individuals which have been dissected out of the maternal uterus, or in examples which have been prematurely aborted. At the moment when the larva leaves the parent, or immediately prior to its birth, the compound stigmata seem to close up completely, the integument becomes intensely black, very strongly chitinised, and impervious to the

strongest beam of light. All that remains of the innumerable stigmata is their external form, the openings being, as far as one can trace, completely fused and obliterated by the closing up and hardening of the integument. On the other hand the sub-lying tracheal trunks remain more or less intact, and can be dissected out of the lobes even in the old effete larval skin which forms the puparium in the succeeding stage in the development of the insect. The paired and relatively large stigmata which lie in the cup-shaped pit remain open, but whether they also remain in vital connection with the nymph or pupa cannot be ascertained in the absence of fresh material. The large ligaments of the anal stigmata can, however, be seen projecting from the lobes into the puparium in well-preserved examples.

Austen (1903) in his description of the puparium ('pupa') says (p. 26) 'the posterior extremity (last segment) is produced on each side into a prominent tumid lip. These lips enclose a deep pit, within which in the larval state were situated the posterior stigmata or respiratory apertures.' He adds also in his more recent publication (1911), 'The tumid lips seen in the larva are equally conspicuous in the pupa, and the shape of the notch between them, in conjunction with the size and shape of the lips themselves affords a valuable means of identifying and distinguishing pupae belonging to different species.' He also figures the puparia of six different species.

Stuhlmann (1907) who gives a very good figure of the larva of '*Glossina fusca*' (= *G. brevipalpis*, Newst.), was of the opinion that the main tracheal system opens into the large cavity of the black, thickly chitinated end of the larva, but gives no details regarding the morphology of these structures.

Roubaud (1909), who ranks as one of the most famous students of the tsetse-flies, gives a very full description of the young larva with excellent drawings but no exact details regarding the true morphological structure of the anal lobes ('protubérances caudales') in the *final larval stage*. He suggests, however, that they function as a protection for the large paired stigmata which lie in the deep cup-shaped pit, thus forming a kind of air chamber favourable to gaseous exchange. He adds also (p. 464), 'Morphologiquement donc, les protubérances caudales, qui sont si caractéristiques des larves de

glossines, sont des appareils de protection des orifices respiratoires, développés aux dépens de la paroi postérieure du segment anal, par des évaginations latérales en ballonnets de l'hypoderme. Les deux orifices stigmatiques les plus externes de chaque côté, distendus et déformés par suite de ce mouvement, se sont trouvés, de plus, oblitérés par la pression des protubérances contre la paroi de l'utérus; ils ont cessé d'être fonctionnels, sacrifiés pour assurer le fonctionnement compensateur du troisième. Il y a donc là encore, un remarquable trait d'adaptation à la vie intra-utérine, spécial aux larves de glossines et qu'il est intéressant de mettre en évidence.'

The above are the more important papers on the subject, though the larvae of tsetse-flies have been referred to by various other authors since Sir David Bruce's (1895) remarkable discovery of the 'pupiparous' habit of these insects in 1895. So far, therefore, as I can trace, no student has hitherto dealt with the morphology of the anal lobes in the adult larva, and their true function has remained an unsolved problem until now.

Having determined the complicated and highly specialized character of the anal respiratory organs in *Glossina*, I proceeded at once to examine the larvae of some of the forest-flies (*Hippoboscidae*) whose anal segments are furnished with lobes of a similar character, though they are not nearly so prominent as those in the larvae of the tsetse-flies (*Glossina*). Having, in the first instance, selected a young adult larva of *Hippobosca maculata*, one of the commonest of the African forest-flies, I discovered that the low-convex anal lobes or callosities were distinctly polypneustic in character, and that the general form and structure of the stigmata and their tubular connections with the large tracheal trunks were very similar to those found in *Glossina*. The only marked difference was that the supernumerary stigmata in *Hippobosca maculata* were much fewer in number (about eighty on each lobe), and that they were arranged in three rather broad, bilateral bands all radiating from the larger paired stigmata which lie in the middle line between the lobes. The larva of the common forest-fly (*H. equina*) of this country has also a very similar arrangement, and so also has *Lynchia maura*.

In the larva of the 'sheep ked' (*Melophagus ovinus*) the respiratory system of the lobes is not nearly so complex and the

number of stigmata is reduced to four on each lobe in addition to the paired stigmata, so that collectively there are five pairs of stigmata. In this species *each lobe* is furnished with a deep cup-shaped pit, near the bottom of which, and occupying a sub-central position, is the anal stigmatic opening which communicates directly with the main abdominal air tubes (tracheae); near the rim or periphery of the pit are two large stigmata: one towards the venter the other towards the dorsum, in addition there is also a very minute pore-like stigma; and outside the pit an outer-lateral stigma rendered most conspicuous by its large and strongly chitinated peritreme. All the stigmata, with the possible exception of the very minute one, are connected together by a thick-walled air sac or trunk, which latter can be easily traced through the integument. Leuckart (1858), in his classical paper on this insect, describes the anomalous character of the stigmata in the adult larva, but in his description and figures (Table III, fig. 9) demonstrates that there are but three stigmata to each lobe; in this he was clearly in error, as there are undoubtedly five in all.

Massonnat (1909), in his extensive memoir on the pupipara, makes no reference to the function of the anal lobes in the larvae, but offers some interesting remarks on the general respiratory system of the larvae and adults. He states (pp. 174, 175) in regard to the latter that in the female the arrangement is a little different from that in the male. In the former there are to be seen an enormous mass of tracheae, which branch out over the uterus. They are divided into two groups: the first arising from the posterior stigmata, the others from the anterior abdominal and from the posterior thoracic stigmata. They all converge towards the middle of the abdomen and cover the uterus with their ramifications. This difference in the arrangement of the breathing organs in the female, he thinks, must certainly have relation to the mode of life of the larva and contribute to its respiration. He states furthermore that the tracheal system of the larva functions by means of the posterior stigmata, the air penetrating through the medium of the maternal vulva, but believes that it should be admitted that the lateral stigmata of the larva also take part in the respiratory interchange. In certain larvae he observed that the lateral (abdominal) stigmata were open, and that owing to the extraordinary abundance of

tracheae in the maternal uterus respiratory interchange between the larva and the mother must take place.

In *Glossina* there is also an abundance of tracheae in the region of the uterus; it is highly probable, therefore, that these organs function in a similar way and contribute to the respiration of the larva during its intra-uterine life, and also that the gaseous exchange is greatly facilitated by the presence of the polypneustic lobes. A study of serial sections will no doubt assist very materially in determining the inter-relationship of the respiratory system between the parent and offspring in both *Glossina* and the Pupipara.

#### CHARACTERS OF THE POLYPNEUSTIC LOBES

*Glossina palpalis*, Robineau-Desvoidy

(Figs. 1 and 2)

*Polympneustic lobes.* Stigmata (fig. 1, *c. st. 1.* profile) covering the whole exterior of the lobes in the form of low, nipple-like protuberances, arranged closely together so that their bases touch each other; collectively reminding one somewhat of the cast or mould of a seamstress's thimble, or individually of the 'nipple-like process' in the puparia of certain scale insects of the genus *Aspidiotus*. Each nipple-like structure has a central stigmatic opening (*c. st. 2.*), the rim of which is circular and very narrowly darker than the integument immediately surrounding it; in some of the openings there are faint traces of hair-like processes projecting into the lumen; these are few in number and are apparently analagous to the setae found in the stigmata of other insects; the thickenings of the integument forming the 'nipple' on the exterior show as two concentric rings; the first is narrow and very close to the opening; the second very broad and extending to the periphery. In many places there is a narrow, pale space between the structures which, when continuous, forms a faintly reticulated pattern.

Several attempts have been made to count the number of stigmata, but owing to their close proximity and regular disposition over the highly convex or rounded surface of the lobes no very definite figures have been obtained; but as all the counts which were made averaged over 500 to each lobe the total number may slightly exceed these figures.

The tubular continuation of each stigma is connected with large branching tracheal trunks (figs. 1, 2, *tr. tru.*), the latter extending across the interior from the outer to the inner lateral walls of the lobes so that they partly fill the interior. These vesicles have no annular thickenings or taenidia, but the walls, nevertheless, appear very rigid, and their surface presents a fine granular appearance

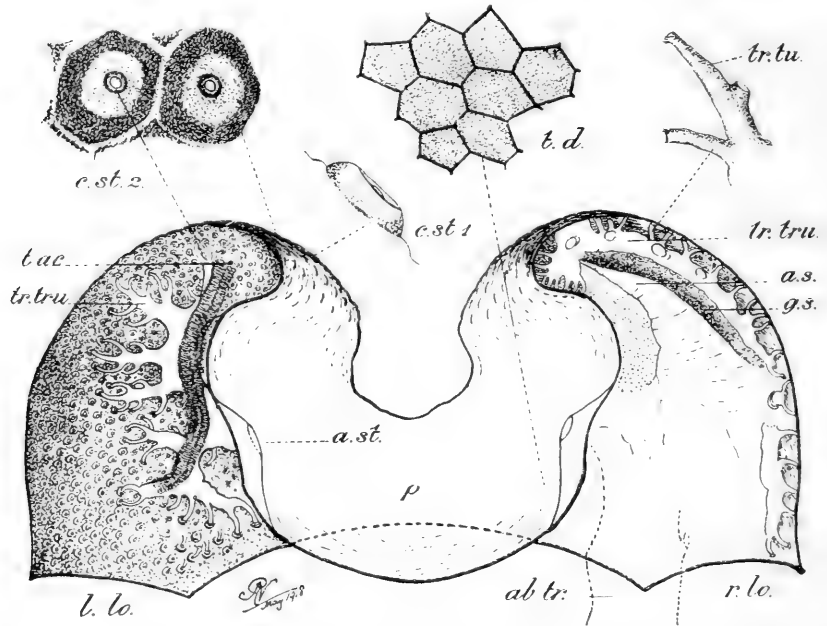


FIG. 1. *Glossina palpalis*: Polypneustic lobes of the young adult larva, seen in longitudinal section in the plane immediately above the paired abdominal stigmata (*a.st.*); *l.lo.*, left lobe; *r.lo.*, right lobe; *p.*, cup-shaped pit between the lobes; *c.st. 2*, compound stigmata as seen by transmitted light; *c.st. 1*, one of the compound stigma as seen in profile; *t.d.*, tessellated dermal cells of the integument, forming the wall of the pit; *tr. tru.*, tracheal trunks with their lateral branches leading to the stigmata in the wall of the lobe; *tae.*, double tracheal tube with incomplete taenidia; *a.s.*, air sac; *g.s.*, granular portion of air sac; *ab. tr.*, relative position of main tracheal tube leading to the abdominal segments.

as if faintly pigmented. In the middle line opposite the region of the terminal, paired abdominal stigmata (fig. 1, *a.st.*) is a large, thin-walled air-sac (fig. 1, *a.s.*), which though ruptured in my preparations seems to be directly connected with the former; it is finely striated transversely on its inner lateral portion and granulated towards the periphery of the lobe (fig. 1, *g.s.*) On



either side of the sac is a double tracheal tube (*tae.*) with apparently incomplete or somewhat irregular taenidia; it lies in the long axis of the lobe, but is imperfect in my preparations, so that its exact course cannot be traced. So far as one can judge, the whole of this very complicated respiratory system of the lobes is connected in some way with the main paired stigmata, but this requires verification, which a further study may give.

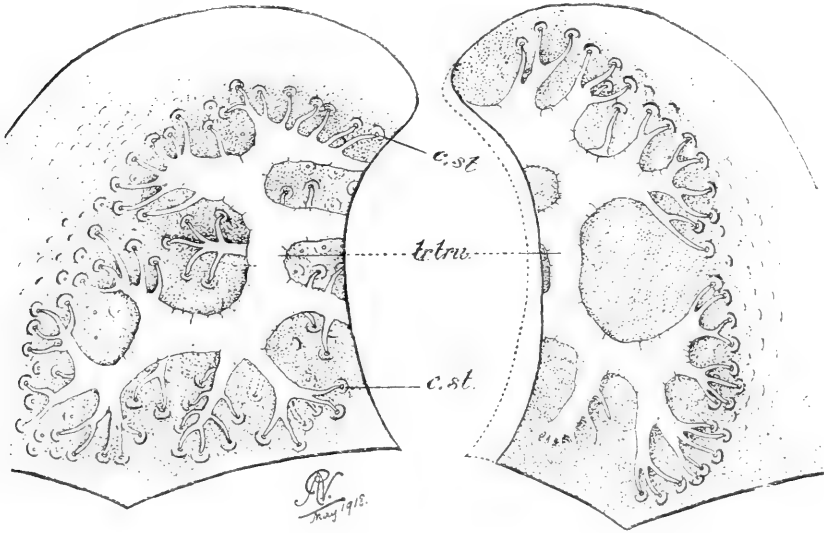


FIG. 2. *Glossina palpalis*: Polypneustic lobes of young adult larva, more highly magnified than in fig. 1, and the cup-shaped pit omitted. Interior, showing tracheal trunks and compound stigmata in two different planes.

. The foregoing description is based upon a single larva dissected from the uterus of the parent.\* The body was divided longitudinally along the medio-lateral line and placed in cold KOH for a few hours and finally mounted in Canada balsam with the cut surfaces uppermost so as to get a clear view of the internal structures of the lobes.

#### *Glossina ? fusca*

(Fig. 3)

The following details are based upon fragments of the lobes which were broken up, in the first instance, in order to study the

\* Captured by Dr. J. Schwetz, Belgian Congo, 1914, to whom I am much indebted for extensive collections of these insects.

integumental character. No very exact particulars of the respiratory system can therefore be given, but I may add that it was the examination of these dissections that led to the discovery of the remarkable respiratory character of the lobes. The larva in question was collected by the late Dr. J. Everett Dutton and Dr. J. L. Todd during their expedition to the Congo Free State in 1904, unfortunately I cannot give its exact specific determination, but it is probably referable to *G. fusca*, Walker. There can, however, be no doubt that it belongs to the '*Fusca* Group' of tsetse-flies as defined by me in the *Bulletin of Entomological Research* (1911); beyond this it is not safe to go, as several closely-allied species occur in the Congo Free State whose larvae await discovery.

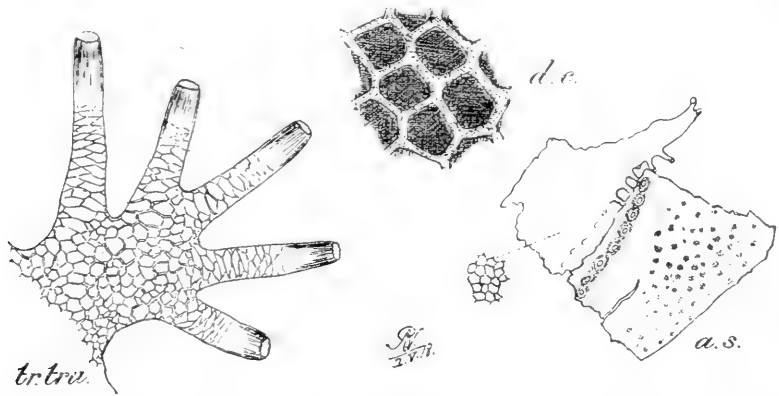


FIG. 3. *Glossina ? fusca*: *d. c.*, tessellated dermal cells of abdomen (from a stained preparation); *tr. tru.*, distal or terminal portion of tracheal trunk with digit-like lateral tubes connected with the stigmata; *a. s.*, air sac, showing the lateral tubes connected with a row of stigmata.

*Polypneustic lobes.* Stigmata circular or ovate arranged, more or less in groups or loop-like series numbering from fourteen to sixteen in each; in places also in definite straight lines or single rows (fig. 3, *a. s.*), the respective rows being widely separated. These 'loop-like' groups are connected with relatively short, stout tubes (tracheae) which branch off from the main trunk, so that when these structures are dissected out with the distal end of the tracheal trunk intact they appear distinctly dactyliform in character (fig. 3, *tr. tru.*). The walls of the tracheal trunks and tubes are strongly and

irregularly reticulated, with the exception of the distal end of the lateral connective tubes at their junction with the stigmata. The tubes connected with the well-defined rows of stigmata (fig. 3, *a. s.*) are similar in form to the others, but they branch off from a relatively very large stiff-walled air-sac (fig. 3, *a. s.*) whose dimensions and exact form I have not been able to determine.

*Glossina morsitans*, Westwood

Three old adult larvae of this species, which were bred from captive flies by Dr. J. B. Davey and myself in Nyasaland in 1910, were dissected. The microscopical examination of these have given very disappointing results, as owing to the density of the chitin I have not been able to discover a trace of the open compound stigmata, even with a beam of strong sunlight passing through the condenser of the microscope. But portions of the main tracheal trunks with their lateral, connective, stigmatic tubes were found. The arrangement of the stigmata, as indicated externally, appear, however, to be very similar to those in *G. palpalis*.

*Glossina ? morsitans*, Westwood

(Fig. 4)

I have also examined a larva bearing the label '*Glossina morsitans*,' but without further data; and although the sculpturing of the lobes was very similar to that in *Glossina morsitans*, Westwood, I am not at all certain that the specimen in question is referable to this species or not. From this example were obtained some relatively large fragments of the tracheal trunks with a few of the lateral tubes intact (fig. 4); but all of these, though treated with KOH in the same way as the others, have remained quite opaque, blackish in colour, very rigid, and almost as hard and brittle as the chitinous walls of the lobes. Whether similar conditions obtain in other species of tsetse-flies I am unable to state. No tracheal organs with such dense and highly chitinised walls as these have been found in the lobes of the puparia of any other specimens of

tsetse-fly hitherto examined. It is possible that the tracheal tubes may harden and thicken simultaneously with the closing of the compound stigmata, but this one cannot at present verify; I therefore record the fact for future reference.

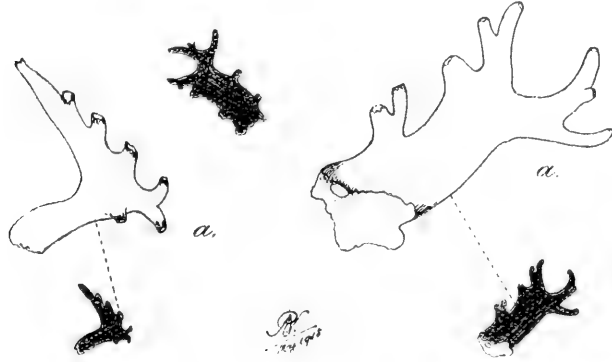


FIG. 4. *Glossina ? morsitans*: Fragments of the highly chitinised tracheal organs dissected from the polypneustic lobes of the larva.

#### PUPIPARA (FOREST-FLIES)

*Hippobosca maculata*, Leach

(Fig. 5)

*Polypneustic lobes.* These, although of considerable dimensions, form but low, convex protuberances with a very shallow depression between them, in which the single pair of abdominal stigmata (fig. 5, *a. st.*) and the micropylar process are placed near the centre. The shallowness of the lobes is, however, of very distinct advantage, as it enables one to examine them in optical section and thereby follow the ramifications of the sub-lying tracheal system with comparative ease, providing always that the integument is sufficiently transparent; such conditions obtain only in young adult larvae dissected from the uterus, as in *Glossina*. Old adult larvae with the dense black chitinous walls to the lobes are useless for an exact study of the respiratory system. The compound stigmata (fig. 5, *c. st.*) are arranged in three broad and well-defined tracks, each series diverging from a point very near to the main anal

stigmata (fig. 5, *a. st.*), and branching bilaterally towards the periphery of the lobe; the openings are small and pore-like and surrounded by three or more concentric rings of darker chitin; the

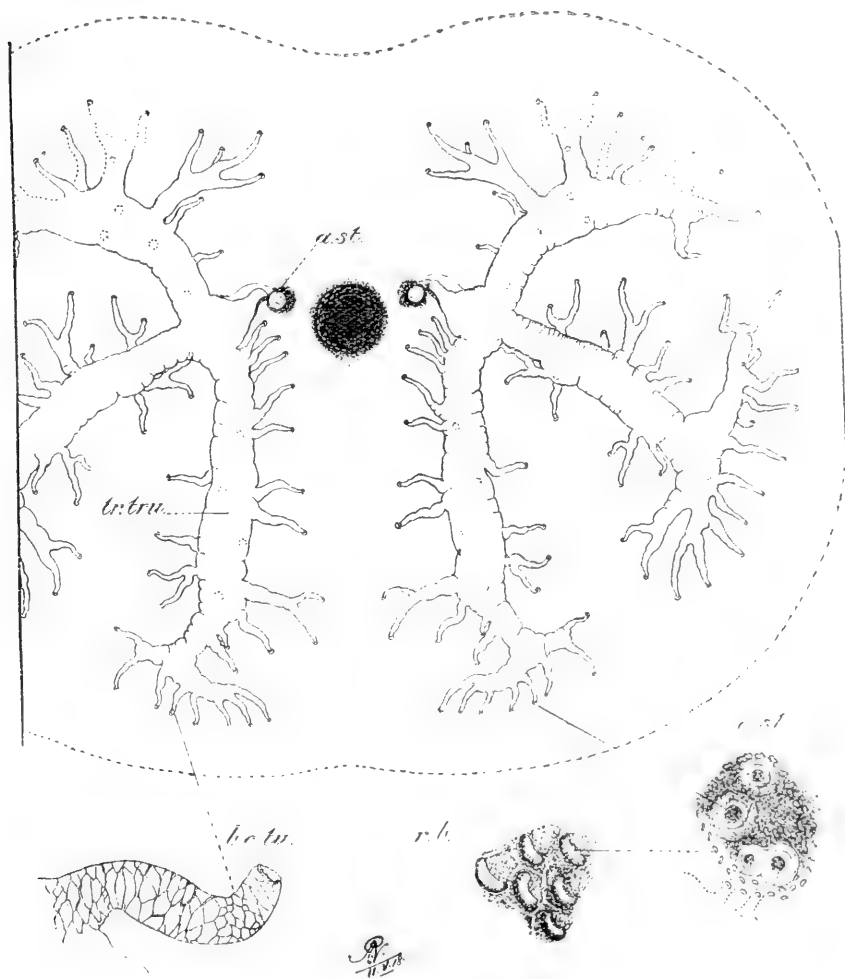


FIG. 5. *Hippobosca maculata*: Polypneustic lobes of the young adult larva; *a. st.*, anal stigmata; *c. st.*, compound stigmata; *r. b.*, reniform thickening of the body-wall; *l. c. tu.*, lateral tube connecting main tracheal trunk with the stigma; *tr. tru.*, tracheal trunk.

spaces between the stigmata rather thickly studded with narrowly reniform thickenings of the body wall (fig. 5, *r. b.*). The tracheal trunks (fig. 5, *tr. tru.*) consist of three large irregularly cylindrical

tubes, so arranged that they lie immediately below the stigmatic openings; these main tubes give off small lateral tubes which for the most part are single, but a few of the longer ones are bifurcated, and each lateral tube is connected with a single stigma. The walls of the tracheal trunks, together with their lateral connective tubes, seem to be relatively thick and rigid, and the surface is strongly but irregularly reticulated. All the main trunks are united proximally, and connected with the main abdominal stigmata by a short commissure, which is really a continuation of the tracheal trunk much attenuated at its union with the paired stigmata. The individual tracheal trunks present a very remarkable appearance, reminding one somewhat of a grotesquely formed or distorted scolopendrid.

*Hippobosca equina*

*Polypneustic lobes.* Very similar in form to those in *H. maculata* and with similarly arranged supernumerary stigmata and tracheal trunks. The details regarding these structures in this species are being worked out, and a description of them will appear in further communications on this subject. New Forest, 1906. (R. Newstead.)

*Lynchia maura*, Bigot

(Fig. 6)

*Polypneustic lobes* with three large bilateral marginal extensions, those on either side of the anus somewhat angular, the others broadly rounded and strongly produced; margin of all extensions strongly undulating or wavy. Anal stigmata occupying a sub-central position with the micropylar process between them. The supernumerary stigmata are relatively small, and number about forty-six on either side; the connective tubes are relatively long, but fairly robust. The tracheal trunks relatively narrow, and consisting of three very widely divergent branches, each branch supplying the stigmata along the wavy margin with lateral connective tubes; the dorsal and ventral branches (*d. l. tru.* and *v. tr. tru.*) have each a backwardly directed branch whose terminal stigmata lie very near to the anal stigmata.

Owing to several large fractures in my preparation I cannot trace the commissure of the tracheal trunks with the main stigmata, but



FIG. 6. *Lynchia maura*: Polypneustic lobes of young adult larva: *d.l. tru.*, dorsal tracheal trunk; *v.tr. tru.*, ventral tracheal trunk. Right side transposed, dotted lines = lines of restoration.

I have indicated its probable course by dotted lines as it is possible that the union of the tracheal trunks with the abdominal tracheal system may be similar to that in *Hippobosca maculata* (fig. 5).

#### *Melophagus ovinus*

(Fig. 7)

*Polypneustic lobes.* The lobes in this species are quite rudimentary though very clearly defined. Near the centre of each lobe is a large, deep, circular and cup-shaped depression; *inside* this pit or open chamber is placed, near the lower portion of the wall, the well-defined main abdominal stigma (*a. st.*), rendered most conspicuous by its clear circular opening; near the edge of the pit

are two slightly larger stigmata (*st. 1.* and *st. 2.*), and one very minute one (*st. 3.*); on the outer lateral side of the pit is another large stigma (*o. lat. st.*), rendered most conspicuous by its large, heavily chitinised peritreme. All the four large stigmata are connected together by a stiff-walled air sac (*a. sc.*) having a finely reticulated surface. Further details of the anatomy of these organs will be given when serial sections have been studied.

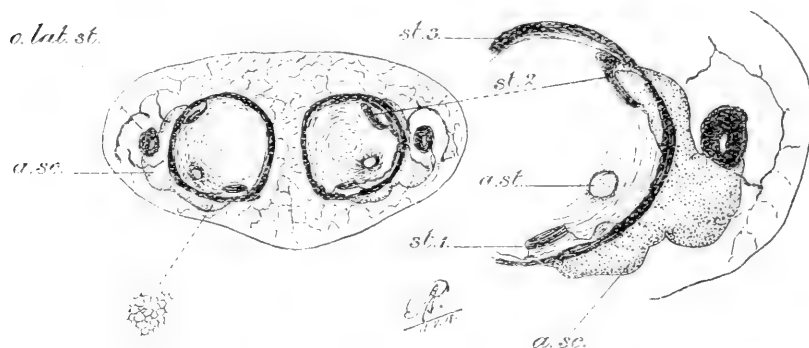


FIG. 7. *Melophagus ovinus*: Polypneustic lobes of young adult larva; *a. st.*, one of the paired abdominal stigmata; *st. 1-st. 3.*, supernumerary stigmata; *o. lat. st.*, outer lateral stigmata; *a. sc.*, connective air sac or trunk.

## CONCLUSIONS

This paper is intended only as a preliminary one, as a further study of the polypneustic lobes of the Glossinae and Hippoboscidae is in progress. There are also other puparia of the *Diptera Cyclorrhapha* possessing similar anal appendages which need investigation, notably several species found in Africa in similar situations to those of *Glossina*: some, in fact, were found in association with *G. morsitans* in Nyasaland (Newstead and Davy). Whether these appendages are in any way homologous\* with those in *Glossina* remains to be seen; a study of them may, however, throw some light on the systematic position of the tsetse-flies. For the moment, however,

\* Two distinct species have now been found to possess polypneustic lobes; but the generic position of these has, so far, not been determined.



it would seem that *Glossina* exhibits very composite characters with a distinct leaning towards the Hippoboscidae. In fact, one may go further and say that the larvae of the two groups, respectively, are so similar in form and structure that, if studied apart from the imagines, one would not hesitate to group them together as members of the same family.

N.B.—The figures of the polypneustic lobes, with the exception of those in fig. 2, are drawn to the same scale.

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# AN INVESTIGATION INTO AN ACUTE OUTBREAK OF 'CENTRAL NEURITIS'

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WITH SIX PLATES

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## I. INTRODUCTION

While the epidemic shortly to be described was in progress, and before the specimens which had been taken to elucidate the morbid anatomy of the condition had been examined, the disease was spoken of as the 'Spanish Town epidemic,' because the majority of cases occurred in the neighbourhood of Spanish Town (St. Jago de la Vega), the ancient capital of Jamaica.

Subsequent enquiries, however, have shown that the condition is also met with in other parts of the island, and, moreover, there is a considerable weight of evidence to support the contention that the 'Spanish Town epidemic' represents the acute stage or an acute onset of a disease which, when it has become chronic, has for a long time been designated in Jamaica as 'Peripheral Neuritis.'

## II. GENERAL HISTORY

Nearly all the patients are adults. Of a large number of cases reported to and seen by me there were but three children, and they were far from typical in the symptoms they exhibited; in fact, it is open to doubt whether they were instances of this condition at all. The youngest patient coming under my personal observation, undoubtedly a case of the condition under review, was a girl of 14 years of age (V.McC., B. 2(b) of the series described later, p. 120).

All of those attacked during the epidemic were of the peasant class, that is, natives who worked as labourers on the sugar estates or who in rare instances had small holdings of their own. Males and females were equally affected. The epidemic started during the cutting and carrying of the cane crop, and the reporting of fresh cases ceased almost abruptly as soon as the crop was finished.

The following is a brief general description of the main features of the condition; differences shown by individual cases will be noticed in the detailed account of such.

In practically every instance the first symptom complained of is a sensation of 'itching in the eyes.' This comes on with comparative suddenness while the patient is at his usual work. In some cases both eyes are attacked about the same time, in others one eye is affected alone at first, and after an interval of varied length, from a few (three to four) hours to as many days, similar sensations are felt in the other eye. At this early stage the conjunctiva is congested and there is photophobia, but not of much intensity. Within the next three days or so the conjunctiva, both ocular and palpebral, is in a swollen, red, oedematous condition, the edges of the lids show abrasions, and small superficial ulcers form with discharge of pus.

Within four days to a week of the onset of the eye symptoms, a burning sensation in the mouth is complained of. This is referred to the mucous membrane of the lips and cheeks, but not as a rule the tongue. The lining membrane becomes red and inflamed and aphthae make their appearance, especially along the edges of the mucous membrane of the lips. At the angles of the mouth a small ulcer or fissure is often present. Salivation is not a common feature.

I noticed it only once in the twenty-one cases detailed, and did not observe it in any of the other patients seen at the hospital, although I saw more than a hundred suffering from this disease.

The soreness of the mouth gives rise to pain on eating for the first twenty-four hours or so; after that, in spite of congestion and ulceration, food is taken without any difficulty or complaint. This soreness is by the patients themselves often attributed to eating sugar-cane.

The affection of the eyes was usually treated by yellow oxide of mercury ointment, and the conjunctivitis cleared up fairly readily. For the stomatitis a mouth-wash containing chlorate of potassium and boric acid soon gave relief.

The above was the sequence of events at the onset in almost every case. One patient stated that the mouth was affected before the eyes, but this was the only exception.

No further symptoms develop during the succeeding week or so, in other words till about fourteen days after the first onset with itching sensations in the eyes. After this interval, however, further symptoms declare themselves, and the cases may be readily placed in one of two categories.

#### 1. *Those with Diarrhoea and Intestinal Symptoms*

These patients have loose actions, increasing in frequency to as many as twenty-five in the day. Of these so affected, some die in a few days apparently from exhaustion, others slowly recover. No treatment seems to benefit the diarrhoea, which appears rather to cease gradually and spontaneously in those who recover. In the latter no further symptoms occur and recovery seems to be complete. The stools are watery and brown in colour.

#### 2. *Those with Nervous Symptoms*

These patients are invariably constipated. As far as I myself observed, and from the histories of a large number of cases reported to me by the medical officer in charge of the hospital (Dr. Redwood White), in all of those exhibiting nervous symptoms constipation was the rule, and, as a corollary to this, in none of the cases belonging to the preceding class (intestinal cases) did any nervous symptoms develop.

The following gives a general résumé of the progress of 'nervous' cases:—

The patient states that he feels a sensation of numbness and tingling, starting in the toes and soles of the feet, occasionally accompanied by a feeling of heat and burning. The numb sensation slowly extends over the dorsum and up the legs to the knees—in some patients to the hips. Both limbs are affected together, and the spread is equal in both; in other words the legs appear to be affected segmentally, symmetrically, and simultaneously.

Some patients state that they feel 'pain in the knees,' but this is only complained of when movement of the joint is carried out. Palpation is quite painless, and there is no heat, redness, or swelling, in fact no objective sign of any joint trouble. With the spread of the numbness walking begins to be impeded, and in the course of three or four days, when the condition has extended to the knees, walking is impossible. The patient can no longer stand unless supported; there is marked incoordination and the patient has practically no control over the lower limbs. When supported and assisted in getting out of bed, the legs are thrown about with wild, exaggerated movements. In some cases, in the intermediate stages between the 'delicate,' unsafe gait of early numbness and the later total inability to walk, the gait is suggestive of that of tabes. Also at this stage there is no real loss of power, the knee-jerks and other deep reflexes are quite abolished, Babinski's sign gives no response normally in a native owing to the horny thickness of the soles caused by walking barefoot. Sense of position is not always, or even often, defective, although spontaneous disposition of the limbs is no longer possible.

In spite of the general complaint of numbness over so large an area, no alteration of sensation could, as a rule, be detected objectively. With the eyes bandaged the responses to finger-touch, cotton-wool, pin-head, and pin-point were correctly estimated and localised. The differentiation between heat and cold, even with a fairly wide range of temperature, was frequently defective. Although no change of sensation, at least no recognisable blunting of the sense of touch, was observable objectively, I noticed more than once in those who were still able to walk that one or both slippers might come off the feet and yet the patient would continue

his progress down the ward without them, or with one on and one off, and not notice the loss until he happened to look down and discover that he had left one slipper behind, when he would return for it.

The difficulty of walking was not made worse by closing the eyes, nor, again, did the patients watch their feet to help their progress. Some cases remained in this condition, but in others a similar sensation of numbness was complained of, after a further interval of one to four days or more, in the finger-tips, spreading rapidly over the palms; while, in a few, the backs of the hands, the forearms, and occasionally the upper arms, were affected also.

In the worst cases there was some difficulty of speech, due, as the patients described it, to numbness of the tongue; in fact, the condition was one of dysarthria and not aphasia. No numbness of the face was mentioned by any of the patients. No alteration of sensation could be detected in upper limbs or tongue by objective tests.

In those cases which terminated fatally, after a considerable period—four to six weeks or more—there was a marked general emaciation; no localised wasting of muscles could be detected at any time. The reaction of degeneration was not found in any instance, though in some there appeared to be a slight alteration in the nature of a less brisk response than normal, but nothing very tangible could be made out.

Some of the patients with nerve symptoms complained, during the early stages, of 'pain in the stomach,' and described this 'as if someone was pulling a rope tight round the chest.' It was clearly of the nature of girdle-pain, and only occurred in the second group of patients—those with nervous symptoms—not in any of those with diarrhoea and intestinal symptoms. This pain was not aggravated by food, in fact, the patients ate well without any discomfort.

The last stage of the fatal nervous cases was always the same. About forty-eight to seventy-two hours before death, when the patients were lying helpless in bed, diarrhoea would set in, and the exhaustion from the combined inanition, emaciation and diarrhoea soon brought about the fatal issue. Even towards the last, though the patient lay helpless and to all appearances totally paralysed, nevertheless there was not in reality a condition of true paralysis,

all movements could be performed, though feebly on account of the emaciation and general state of exhaustion.

Certain residual symptoms were noticeable in some of those who recovered after a considerable period of illness. These were in the main :—

1. Dimness of vision, usually spoken of as 'a darkness in front of the eyes.'
2. A certain degree of deafness, which usually increased as time went on, although the other symptoms might clear up almost completely.
3. A peculiar steppage gait, but without drop-foot, an exaggeration of movement of the legs but without the tabetic stamp; not, as a rule, with a wide base.

### III. DESCRIPTION OF INDIVIDUAL CASES

#### A. INTESTINAL FORM

##### 1. *Mild cases with recovery.*

(a) D.J., male, aged 35 years. This man was first taken ill on March 14th, 1917, with 'burning and itching of the mouth and tongue' and sores at the angles of the mouth. For the first two days the mastication of food was painful, so that he could only take soft, semi-fluid food in the form of 'pap' (cornmeal, arrowroot); after that time he could take ordinary food without any pain or discomfort. A week later, March 21st, his right eye began to "burn and itch" and four days afterwards the left eye was similarly affected. He stated he had been at work earning fair wages, and had been having 'plenty of good food.' He did not complain of any numbness or tingling and on examination showed no evidence of any nervous symptoms. There were no physical signs of any disease in heart, lungs, or abdominal organs. The bowels were inclined to be loose, but not very frequent, three or four motions daily. The urine was normal, the faeces showed the presence of ova of ankylostoma, ascaris, and trichiuris. When again examined on April 12th his condition was practically the same, and no nervous symptoms had developed. By the 25th he was much improved, mouth and eyes were well, no symptoms referable to the nervous system had appeared, and the patient left the hospital quite well a day or two later.

This was an exceptionally mild case and the mouth was attacked before the eyes, thus differing in onset from the rest of the cases, but otherwise the initial symptoms were typical. The presence of helminthiasis is of little significance, for the vast majority of the labourers in Jamaica harbour them, as reports made by me officially on various occasions during the last five years have shown.

Examination of blood from this case, carried out on March 28th, yielded the following results :—



Erythrocytes 3,940,000 per c.mm. Occasional nucleated red cells seen; no abnormalities in shape, slight degree of anisocytosis. Haemoglobin 70 per cent. Colour Index 0.89.

Leucocytes 8,400 per c.mm. Differential count of these gave:—

Polymorphonuclears	...	...	...	...	54.4 per cent.
Myelocytes	...	...	...	...	1.0 „
Metamyelocytes	...	...	...	...	0.2 „
Eosinophiles	...	...	...	...	3.8 „
Basophiles	...	...	...	...	0.4 „
Large Mononuclears	...	...	...	...	1.0 „
Transitionals	...	...	...	...	0.6 „
Lymphocytes: large	...	...	...	...	4.6
small	...	...	...	...	32.8
Rieder type	...	...	...	...	1.2
					— 38.6 „

An Arneth count on this blood gave:—

I	II	III	IV	V	S (Stabkernige)
9.9	40.4	32.4	12.2	2.2	2.9

Arneth Index 66.5.

On April 12th 1917 there was a reduction in the percentage of polynuclear leucocytes with an increase in the eosinophiles and the large mononuclears; the details of the count on that date were:

Polymorphonuclears	...	...	...	...	43.0 per cent.
Promyelocytes	...	...	...	...	0.2 „
Myelocytes	...	...	...	...	1.2 „
Metamyelocytes	...	...	...	...	—
Eosinophile Myelocytes	...	...	...	...	0.4 „
Eosinophiles	...	...	...	...	9.2 „
Basophiles	...	...	...	...	0.8 „
Large Mononuclears	...	...	...	...	3.6 „
Transitionals	...	...	...	...	1.6 „
Lymphocytes: large	...	...	...	...	7.6
small	...	...	...	...	29.8
Türk's	...	...	...	...	1.0
Rieder type	...	...	...	...	1.6
					— 40.0 „

An Arneth count on this date gave:—

I	II	III	IV	V	S
3.7	36.4	35.3	13.9	3.2	7.5

The Index being 57.7.

Lastly, on April 25th the polymorphonuclears showed a still further reduction relatively, and the large mononuclears an increase, the remainder being almost the same as when the count was made on April 12th :—

Polymorphonuclears	...	...	...	...	36.6 per cent.
Promyelocytes	...	...	...	...	0.4 „
Myelocytes	...	...	...	...	0.8 „
Metamyelocytes	...	...	...	...	0.6 „
Eosinophiles Myelocytes	...	...	...	...	0.4 „
Eosinophiles	...	...	...	...	9.8 „
Basophiles	...	...	...	...	2.4 „
Large Mononuclears	...	...	...	...	4.8 „
Transitionals	...	...	...	...	3.8 „
Lymphocytes : large	...	...	...	7.4	
small	...	...	...	30.4	
Türk's	...	...	...	0.2	
Rieder type	...	...	...	2.4	
				—	40.4 „

Arneth count :—

I	II	III	IV	V	S
6.5	37.1	32.2	13.8	3.6	6.8

Arneth Index 59.7.

(b) J.S., male, aged 44 years. This man stated he was quite well and at work until March. 22nd, 1917, when his right eye began to 'itch and burn.' The following day the left eye was similarly affected and his mouth was sore, but the latter was at no time severe enough to prevent him from taking food.

When seen by me on March 28th the right eye was a little congested, like a case of ordinary catarrhal conjunctivitis; the left was in a more severe state of inflammation, especially towards the inner canthus which was swollen and deeply injected.

He was inclined to have loose actions of the bowels for the previous two or three days. No nerve symptoms of any kind complained of or discovered on physical examination. The condition of the eyes and mouth remained the same for ten days or so, and then improvement set in, and when examined again on April 12th the right eye was normal, the left still a little injected. The diarrhoea had increased somewhat and he was having five or six loose actions daily. Still no nerve symptoms present. By the 25th the eyes and mouth were quite well, the diarrhoea had ceased, usually only one motion a day, occasionally two, but not loose. Examination of the urine of this patient showed that with the exception of some amorphous urates this excretion was normal. The faeces when first seen contained some pus and red corpuscles. A few cysts of *Entamoeba tetragena* were present, and cultivation yielded a growth of *Bacillus pyocyaneus*. Also while making a differential count of the leucocytes in this patient's blood a malarial crescent was seen; no intracorpuseular parasites detected. In spite of all these things the temperature never rose above 100° F. He left the hospital quite recovered on April 28th.

A differential count of this patient's leucocytes yielded the following results on March 28th, 1917.

Polymorphonuclears	...	...	...	...	46.4 per cent.
Promyelocytes	...	...	...	...	1.2 "
Myelocytes	...	...	...	...	2.2 "
Metamyelocytes	...	...	...	...	1.0 "
Eosinophiles	...	...	...	...	2.2 "
Basophiles	...	...	...	...	1.4 "
Large Mononuclears	...	...	...	...	4.0 "
Transitionals	...	...	...	...	2.4 "
Lymphocytes : large	...	...	...	...	5.4
small	...	...	...	...	30.8
Türk's	...	...	...	...	0.8
Rieder type	...	...	...	...	2.2
					— 39.2 "
Arneth count :—					
I	II	III	IV	V	S
15.1	44.4	25.8	8.2	2.2	4.3
Arneth Index 72.4.					

A second examination on April 12th revealed very little change :—

Polymorphonuclears	...	..	...	...	47.2 per cent
Promyelocytes	...	..	..	...	0.6 "
Myelocytes	..	...	...	...	2.8 "
Metamyelocytes	...	...	...	...	1.6 "
Eosinophiles	...	...	...	...	0.4 "
Basophiles	...	...	...	...	1.2 "
Large Mononuclears	...	...	...	..	3.6 "
Transitionals	...	...	...	...	0.8 "
Lymphocytes : large	...	...	...	...	6.0
small	...	...	...	...	31.4
Türk's	...	...	...	...	1.0
Rieder type	...	...	...	...	3.4
					— 41.8 ..
Arneth count :—					
I	II	III	IV	V	S
13.6	50.4	22.0	7.6	1.3	5.1
Arneth Index 75.					

## 2. Severe case of intestinal form.

J.A., male, aged 30 years. In normal health until April 2nd when his eyes started to itch, and within 24 hours became red and inflamed and he could not bear the light. During the succeeding 48 hours the lids became sore and 'matter stuck them together during sleep,' but in the day-time there was very little discharge. A few days later—four or five, so far as he remembered—the mouth became sore. The bowels had been acting normally all this time and until the 18th when the actions became loose and frequent. On account of the soreness of eyes and mouth and the diarrhoea, he presented himself at the hospital on April 22nd and was admitted.

When seen on the 25th the eyes were much better ; there were no abrasions of the lids, but still some muco-purulent discharge in the folds of the conjunctiva and at the inner canthus. The general stomatitis had subsided, but there were small ulcers at the angles of the mouth. Bowels were still loose : he had had 7 to 11 actions daily since admission.

There were no nerve symptoms complained of, and none detected on minute examination. There was no history of any Yaws. The pus from the eyes yielded colonies of staphylococcus, micrococcus catarrhalis, and some Gram-positive rods of diphtheroid arrangement. The cells showed no inclusions of any sort. The blood was taken and a Wassermann reaction carried out, but the result was totally negative. Lumbar puncture was performed and cultures of the spinal fluid put up on various media—agar, nutrose-ascitic-agar, hydrocele-agar, blood-agar, and blood-serum (Löffler)—but all remained sterile and nothing abnormal was discovered in smears made from the fluid after centrifugalization; there was no deposit. Albumen not in excess.

The blood-count in this case gave the following results:—

Polymorphonuclears	...	...	...	...	56.6 per cent.
Promyelocytes	...	...	...	...	1.0 "
Myelocytes	...	...	...	...	1.2 "
Metamyelocytes	...	...	...	...	1.2 "
Eosinophiles	...	...	...	...	3.2 "
Basophiles	...	...	...	...	1.8 "
Large Mononuclears	...	...	...	...	3.0 "
Transitionals	...	...	...	...	2.2 "
Lymphocytes: large	...	...	...	...	6.2
small	...	...	...	...	21.2
Türk's	...	...	...	...	0.6
Rieder type	...	...	...	...	1.8

— 29.8 "

Arneth count:—

I	II	III	IV	V	S
17.0	40.9	25.5	7.4	5.0	4.2

It will thus be seen that when the patient was at his worst the Arneth Index was unduly high, viz., 70.6. I regret that this patient left before another opportunity arose for taking his blood again.

Before passing on to a detailed description of the nervous form of this condition, the following case deserves mention because in the early stage it was like the nervous variety and during that time was accompanied by constipation, but later developed intestinal symptoms with total arrest of the nervous system affection and terminated fatally in a manner similar to that already related. The case was reported to me by Dr. White; it did not come under my personal observation. The history is not so complete as one would wish, as no details of the nervous system condition were stated. It is given here for what it may be worth, as linking the first group with the reports of the nervous cases which follow.

C.D., female, aged 23 years. In the early days of April 1917 her 'mouth became sore and ulcerated.' On the 11th she felt numbness and tingling in the toes and feet, gradually extending up the legs. On April 25th, when she could no longer walk unaided, she was brought up to hospital and was admitted. During the first few days she had loose but not frequent actions of the bowels, while the fortnight prior to admission (11th—25th, the period of spread of the tingling and numbness) she had been very constipated. Temperature on admission was 101° F.; it never rose above this and on the 25th had fallen to 99° F.; subsequently until her death on May 4th the temperature remained normal.

She lived for nine days after coming to hospital, and during this time there was no extension of the numbness or tingling and no further development of any

fresh nerve symptoms; diarrhoea, however, replaced the constipation, the number of actions varying from five to eleven daily, loose, brown and watery. No treatment seemed to be of any avail for this, and the patient died, as stated above, on May 4th.

## B. NERVOUS SYSTEM CASES

### 1. *Mild with recovery.*

H.B., female, aged about 30 years. Towards the end of February, 1917, according to the history given by this patient, her left eye started to itch and became inflamed so that she could not bear the light. A week later the right eye was attacked with 'watering and burning.' Some four days later her 'mouth became sore.' On March 12th she first felt 'cramps' in her feet. Questions elicited the fact, in this and several other patients subsequently, that 'cramps' meant tingling and numbness, and nothing resembling what one usually understands by the term cramps. The toes were first affected and during the succeeding week these sensations extended as far as the knees. Both lower limbs were affected together. She had suffered greatly from constipation since the first week in March; up to that time she had always been very regular.

This patient was first seen and examined by me on March 28th, the third day after her admission to hospital. Her eyes and mouth were inflamed, but no ulcers could be discovered. There was distinct photophobia. She walked 'delicately,' not with a gait characteristic of any known condition, but most resembling one with corns or sore feet. She stated that the ground 'felt soft.' The knee-jerks were present, no loss of power could be detected in any of the leg movements. In spite of the complaint of numbness, by objective tests sensation appeared to be normal—wisp of cotton-wool, pin-head, pin-point, light finger-touch all felt and accurately localised with eyes bandaged. There was, however, some defective appreciation of difference between heat and cold. About six times out of ten heat was described as cold, never *vice versa*. All the reflexes were normal; no Romberg's sign, no ataxia, no loss of sense of position. The urine was normal; the faeces contained ova of ankylostome and ascaris. All her symptoms improved rapidly and she was able to leave the hospital on April 7th.

### 2. *Slightly more severe cases with recovery.*

(a) E.S., female, 27 years of age. Working and in normal health until March 14th when she noticed suddenly a 'burning and itching' in her eyes; both eyes were attacked almost simultaneously. There had been no soreness of the mouth. No further symptoms developed during the next ten days, but on March 24th she began to have a sensation of numbness in her toes; this numbness had extended to the knees by the 28th and she stated that the knees were painful, but only on movement of full extension or flexion. She complained also of 'pain in the chest as if a cord were tight round the stomach.' (The 'chest' of the native is below the belt). Her bowels had been obstinately constipated throughout the illness.

State when examined on March 28th: In spite of the extensive area of numbness complained of, no alteration of sensation could be detected by objective tests. Deep reflexes were absent, the superficial were variable. On standing there was distinct ataxia, more of a swaying character and a tendency for the legs

to double up, although there was no apparent loss of power in any of the leg movements when she was lying down or sitting on the edge of the bed. The patient was just able to walk alone, but for safety slight support was given; the gait was not tabetic (the medical officer stated that it had been when the patient first came in), but there was an irregular swinging of the legs and feet. The patient stated on this occasion that the knees were painful when at rest as well as on movement, but examination revealed nothing wrong, no swelling, no heat, no pain on palpation, and the movements of the joint were free.

The urine contained some amorphous urates and crystals of calcium oxalate, but was otherwise normal. The faeces contained ova of ankylostoma and trichiuris.

Blood-smears were taken and the following differential count obtained:—

Polymorphonuclears	...	...	...	...	27.2 per cent.
Promyelocytes	...	...	...	...	0.8 "
Myelocytes	...	...	...	...	0.8 "
Metamyelocytes	...	...	...	...	0.6 "
Eosinophiles	...	...	...	...	5.0 "
Basophiles	...	...	...	...	0.6 "
Large Mononuclears	...	...	...	...	3.2 "
Transitionals	...	...	...	...	1.6 "
Lymphocytes: large	...	...	...	...	7.4
small	...	...	...	...	49.8
Türk's	...	...	...	...	—
Rieder type	...	...	...	...	3.0
					60.2 "

The Arneth count on the same specimen gave:—

I	II	III	IV	V	S
6.6	38.9	29.5	16.9	4.4	3.7
Arneth Index 60.2.					

When seen again on April 12th her condition was certainly improving; she could walk alone with much less difficulty. She stated that the tightness in the chest had almost gone, and her eyes were practically well. She left hospital 'feeling quite well again' on April 16th and the medical officer states that he could not make out any residual effects of the illness. The very low percentage of polymorphonuclear leucocytes during the height of the illness is worthy of note.

(b) V. McC., female, aged 14 years, daughter of the case next to be related. This girl lived with her mother, but was not taken ill until about a month after the onset of the mother's attack. She stated that she could not remember whether there had been anything wrong with her eyes, but she knew that towards the end of March her mouth became sore and ulcerated, and during the next five to seven days eating was painful and difficult. A week after the mouth became sore she noticed a numbness of the feet, and during the succeeding week this sensation spread up as far as the knees; it never extended beyond this, and her hands were not affected at all. She was somewhat constipated but not markedly so. After these symptoms had persisted in practically the same condition, neither better nor worse, for a month, a gradual improvement set in and now (June 22nd) she 'feels much better.' Bowels regular.

On examination on this date she was able to walk without any difficulty, and she stated that 'the numbness had nearly gone but not quite.' Nothing abnormal detected on testing with wool, pins, touch, etc., as in the other cases. The only symptom which was giving any trouble was a 'darkness of the eyes.' This appeared to mean a haziness of vision and was mainly present when the patient

went out of doors into the bright sunlight. She noticed it very little while in a room, away from any glare, but stated that when she tried to read, the print after a little while tended to become blurred and the letters to run together.

Reaction to convergence seemed to be a little sluggish, but nothing else abnormal could be detected. Ankylostoma ova present in the faeces.

Smears of her blood were taken for subsequent examination and gave the following results:—

Four erythroblasts were seen while counting the 500 leucocytes, and three benign tertian malarial parasites.

Differential leucocyte count:—

Polymorphonuclears	...	...	...	...	37.4 per cent.
Promyelocytes	...	...	...	...	0.8 "
Myelocytes	...	...	...	...	1.6 "
Metamyelocytes	...	...	...	...	1.2 "
Eosinophiles	...	...	...	...	8.2 "
Basophiles	...	...	...	...	0.4 "
Large Mononuclears	...	...	...	...	4.6 "
Transitionals	...	...	...	...	2.8 "
Lymphocytes: large	...	...	...	...	7.2
small	...	...	...	...	33.8
Türk's	...	...	...	...	1.8
Rieder type	...	...	...	...	0.2

Arneth count:—

I	II	III	IV	V	S	
6.4	42.8	38.0	4.8	1.1	6.9	43.0 "

Arneth Index 68.2.

The large mononuclear increase may be ascribed, in part at least, to the malaria present. The relative eosinophilia was probably due to the presence of ankylostomes.

3. *Moderately severe case with partial recovery*; that is, recovery of general health, but with residual symptoms.

A.B., female, aged 33 years, mother of the patient last described. The history in this case was not remembered very accurately in detail, but her illness had begun four months prior to my seeing her. She was taken ill one day towards the end of February with soreness of the eyes and mouth. The eyes were first attacked with burning and itching; the mouth shortly afterwards. The patient could not remember whether the eyes were attacked together, but, if not, the interval was short; nor could she state what length of time elapsed before the mouth became involved. About a week after the latter, however, she felt a sensation of numbness in the feet, spreading gradually up the legs to the hips. In a few days more the hands became numb, the fingers being first affected, then the palms before the backs.

This condition remained practically unchanged for two months or so. At the beginning of May a gradual improvement set in, the hands regaining their normal feeling first. Ability to walk began to return towards the end of May, and when seen on June 22nd she was able to walk fairly well and stated that the numbness had nearly gone and she 'felt natural' except that her eyes were 'a little dark.' Questioning her more exactly as to what she implied by this, I was told that objects in the bright sunlight were dim, and when she was indoors she found sewing difficult and reading still more so.

The bowels had been obstinately constipated all through the illness. No alteration of sensation could be detected by the usual tests; the knee-jerks were absent, and the walk was suggestive of 'steppage gait' but without drop-foot or with very slight drop. The stools contained hookworm ova in considerable numbers. Examination of the blood of this patient showed the presence of the ring forms of *Plasmodium falciparum*; occasional erythroblasts were seen, three during the counting of 500 leucocytes. The differential count of the latter gave:—

Polymorphonuclears	...	...	...	...	33.8	per cent.
Promyelocytes	...	...	...	...	0.8	"
Myelocytes	...	...	...	...	1.2	"
Metamyelocytes	...	...	...	...	1.0	"
Eosinophiles	...	...	...	...	18.0	"
Basophiles	...	...	...	...	0.6	"
Large Mononuclears	...	...	...	...	6.6	"
Transitionals	...	...	...	...	4.6	"
Lymphocytes: large	...	...	...	9.2		
small	...	...	...	21.8		
Türk's	...	...	...	1.8		
Rieder type	...	...	...	0.6		
				—	33.4	"

Arneth count:—

I	II	III	IV	V	S
3.0	39.1	37.3	11.8	3.5	5.3

Arneth Index 60.7.

The increase in eosinophiles is probably ascribable to the fact of the patient harbouring ankylostomes, the increase in mononuclears and transitionals to the malarial condition (some of the monocytes showed pigmentation). Apart from these the low polymorphonuclear percentage is worthy of note and may be compared with that of the preceding case (her daughter).

4. *Severe case with recovery of general health but with residual nerve symptoms.*

(a) E.M., female, aged 36 years. Her illness began suddenly 'about the middle of March,' with pain and itching in the eyes; the pain was of a burning, smarting character, and she was unable to bear the daylight. Both eyes were affected together, and in a few hours they became bloodshot. Four days later her mouth became sore, and for 24—48 hours eating caused pain, but after that she was able to take her ordinary food (cane, at that time, and some yam) with little if any discomfort.

On March 29th her feet began to feel 'burning and numb'; both were affected together. This sensation started in the toes and soles and gradually spread upwards to the knees or a little above. On April 5th the same numb sensation began in the finger-tips and when seen a week later, on April 12th, the palms were affected also, and she thinks 'the backs of the hands do not feel quite right.' She also complained on this day that her 'chest felt tied up.' On examination:—Her walk was not characteristic of any definite condition, the gait may rather be described as stiff and stilted and was not tabetic. She stated that the ground felt 'like india-rubber.' The knee-jerks were absent, superficial reflexes mostly normal, but varied a little at different testings. Babinski's sign not obtained (skin of sole very thick), but on deep pressure the whole limb was drawn up, no dorsiflexion of the toes noticed. No alteration of sensation could



be made out by the usual tests. Examination of the cerebro-spinal fluid revealed nothing abnormal, very few cells were present, the majority were mononuclears; no growth was obtained from attempts at culture on various media; albumen not in excess. Wassermann reaction carried out with the fluid was negative, as also was the test with her blood-serum.

The other results of the blood examination were:—

Polymorphonuclears	...	...	...	...	37.4 per cent.
Promyelocytes	...	...	...	...	0.4 „
Myelocytes	...	...	...	...	1.6 „
Metamyelocytes	...	...	...	...	0.6 „
Eosinophiles	...	...	...	...	4.2 „
Basophiles...	...	...	...	...	0.6 „
Large Mononuclears	...	...	...	...	4.6 „
Transitionals	...	...	...	...	1.8 „
Lymphocytes: large	...	...	...	9.8	
small	...	...	...	35.6	
Türk's	...	...	...	1.0	
Rieder type	...	...	...	2.4	
				—	48.8 „

Arneth count:—

I	II	III	IV	V	S
9.1	53.0	21.4	9.6	3.2	3.7

Arneth Index 72.8.

No nucleated red cells seen; no malarial parasites, no pigmented mononuclears. No ankylostomes or ova of any helminth seen in the faeces.

This patient was seen again on April 25th; she stated then that the feeling of tightness of the chest was worse, but that the other symptoms had improved. She described the sensation in the feet then as being 'tightened up but not so numbed.' She could not explain more definitely what she meant by this, and I am not able to conjecture. She denied that the feeling at all resembled ordinary cramps. She walked quite as well, and, in my opinion, better and less stiffly than on the 12th.

The blood examination on this occasion gave results very little different from those of the 12th.

Polymorphonuclears	...	...	...	...	41.2 per cent.
Promyelocytes	...	...	...	...	0.4 „
Myelocytes	...	...	...	...	0.8 „
Metamyelocytes	...	...	...	...	0.6 „
Eosinophiles	...	...	...	...	4.0 „
Basophiles...	...	...	...	...	1.2 „
Large Mononuclears	...	...	...	...	3.8 „
Transitionals	...	...	...	...	2.8 „
Lymphocytes: large	...	...	...	8.4	
small	...	...	...	33.2	
Türk's	...	...	...	1.6	
Rieder type	...	...	...	2.0	
				—	45.2 „

Arneth count:—

I	II	III	IV	V	S
5.8	47.1	35.4	7.8	1.5	2.4

Arneth Index 70.6.

She remained in hospital for some time afterwards, but very little further improvement took place and she left. I was unable to find out her residence and therefore cannot state what progress, if any, took place subsequently.

(b) C.S., female, aged 30 years. This patient was admitted to hospital on April 14th, and gave the following history; early in April (she is not certain of the date) her eyes and mouth became 'itching and sore.' The eyes were both affected together a few hours before the mouth became involved. She suffered from constipation. No other symptoms made their appearance till April 12th when she felt her toes and feet becoming numb; as this sensation continued to spread she came to the hospital, as already stated, on the 14th. Since that date the condition has extended to the knees, and when seen on the 25th she said that in addition to these symptoms in the legs she had a 'sense of tightness round the chest.' 'On examination it is noticed that she can walk fairly well, lifting the feet as in a modified steppage gait, but requires some support, saying that she feels unsteady owing to the ground feeling soft. Knee-jerks are absent; Romberg's sign is not present; though unsteady in walking, she can stand fairly well, and closure of the eyes does not affect this. Pupils react normally to light and convergence. By objective tests no alteration of sensation is made out in the numb area, and there is no hyperaesthetic zone at the level of the girdle sensation.'

Cerebro-spinal fluid was taken, smears made and various culture-media inoculated with the fluid, but no growth occurred, and nothing abnormal was seen in the original smears, nor in those made after centrifugalization of the fluid.

The Wassermann reaction was carried out with both this fluid and the blood, but the result was totally negative with both.

Blood examinations gave :—

Polymorphonuclears	...	...	...	...	43.0 per cent.
Promyelocytes	...	...	...	...	0.2 "
Myelocytes	...	...	...	...	0.8 "
Metamyelocytes	...	...	...	...	0.8 "
Eosinophiles	...	...	...	...	4.0 "
Basophiles	...	...	...	...	1.8 "
Large Mononuclears	...	...	...	...	3.6 "
Transitionals	...	...	...	...	2.4 "
Lymphocytes : large	...	...	...	11.6	
small	...	...	...	29.6	
Türk's	...	...	...	1.4	
Rieder type	...	...	...	0.8	
				—	43.4 "

Arneth count gave :—

I	II	III	IV	V	S
6.5	42.3	25.6	13.0	3.7	8.9
Arneth Index 61.6.					

No nucleated red cells seen, no malarial parasites or pigmented mononuclears. Faeces and urine normal, no helminth ova present in the former.

(c) R.H., female, aged 42 years. This patient gave the following history : She was quite well until May 23rd, 1917, when, while she was at work on the sugar estate, her right eye began to itch. The next morning the lids were stuck together on waking and the light caused pain. That day the left eye became similarly affected, and two days afterwards her mouth became sore and she could take food

only with pain and difficulty. White patches and superficial ulcers formed on the lips and tongue. On June 2nd, ten days after the onset, her 'feet began to burn'; the toes and soles of the feet were first attacked, but the sensation rapidly spread, reaching as high as the hips in another week; both were affected together and equally. Within 24 hours of onset the sensation of burning was replaced by numbness. On June 9th there was a 'tight feeling' round the lower part of the abdomen, and, by this date, walking, which had become increasingly difficult, became impossible and when attempting to walk she fell. She had been constipated from the beginning of her illness, though up to that time her bowels had always acted regularly. On June 10th her finger-tips felt numbed (without any preceding burning) and this sensation spread over the palms and dorsa as far as the wrists, but no further. Moreover, the affection of the hands was much slighter than in the feet and legs, and after persisting for a week, improvement in sensation in the hands set in.

I saw her on June 22nd, and found the hands were, as she stated, nearly well. She could pick up a pencil between a finger and thumb, except with the little finger of the right hand. The lower limbs had also considerably improved, and she was able to walk unaided, but slowly with a spastic gait, the feet, as it were, sticking to the floor. She stated that the ground felt soft. The knee jerks were not elicited, but the quadriceps was felt to contract when the patellar tendon was tapped. She was able to stand without difficulty with her eyes closed, and the walking was not made appreciably worse when they were bandaged. There were no signs at all of any pellagrous condition.

By the usual tests no alteration of sensation could be detected, except an irregularity in the interpretation of heat and cold. She stated that her eyes were 'a little dark'; this, she explained by saying that sewing was difficult (not on account of any numbness of the fingers, but owing to her not seeing the stitches clearly), and on attempting to read the letters ran together and the print became blurred. Though she did not complain of deafness, I am of opinion that there was a slight degree of difficulty of hearing, evidenced by her turning her head to concentrate her attention to the direction of the voice, when questioned. Her friends also thought she was 'a little hard of hearing since her illness.'

Her blood was taken and gave the following results of a differential leucocyte count:—

Polymorphonuclears	...	...	...	...	30.6 per cent.
Promyelocytes	...	...	...	...	0.4 "
Myelocytes	...	...	...	...	0.8 "
Metamyelocytes	...	...	...	...	0.2 "
Eosinophiles	...	...	...	...	15.4 "
Basophiles	...	...	...	...	0.4 "
Large Mononuclears	...	...	...	...	2.2 "
Transitionals	...	...	...	...	1.0 "
Lymphocytes: large	...	...	...	...	8.6
small	...	...	...	...	39.0
Türk's	...	...	...	...	1.0
Rieder type	...	...	...	...	0.4
					— 49.0 "

Arneth count:—

I	II	III	IV	V	S
6.6	45.7	27.5	12.4	1.9	5.9

Arneth Index 66.05.

No malarial parasites were seen, nor any pigmented mononuclears; one erythroblast was observed in making the count. The eosinophilia is explicable by the fact that the faeces contained ova both of *Ankylostoma duodenale* and of *Ascaris lumbricoides*.

##### 5. *Severe and chronic cases.*

(a) E.G., female, aged about 20 years. States that she suffered from an attack of Yaws as a child, but there are no signs of that disease to be seen now, unless an unpigmented patch and a scar on the right wrist are taken as evidence of this. The patient states that she was well until April 19th, when her left eye began to itch and soon after became red, and she could not bear the light with that eye. Some 24 hours later the right eye was similarly affected. The mouth was also sore, but the patient does not remember with certainty the exact chronological sequence of events at the onset. At one time she stated that there was an interval of a week between the eye and mouth involvements, at another that they were affected almost at the same time. She had not felt any pain on eating at any time since her illness began, not even when the mouth became sore.

A fortnight 'or thereabouts' after the onset—that is, on or about May 2nd—her toes and the soles of her feet began to feel numb, and, as she described it, 'like needles pricking and worms crawling there.' These sensations spread over the dorsum of each foot and at this time when she walked she 'felt as if walking up in the air.' Walking became increasingly difficult and on May 10th she fell down on the road. She had no convulsions or any loss of consciousness, as far as can be ascertained, and she got up immediately unaided and walked home. She took some time to get back, saying that her legs and feet 'felt heavy, but not tired.' After that date she no longer attempted to walk out of doors, and at home she experienced greater and greater difficulty in moving about. This inability progressed so rapidly that by the 13th or 14th May she had to move about her room on hands and knees, and finding that she could not climb into her bed, she had the bed made up on the floor. By this time the numbness, tingling and formication had extended to the hips. The trunk does not appear to have been affected, at all events she denied feeling any of these sensations there, nor was there anything suggestive of a girdle pain. On the 18th May she felt the tingling and numbness in the tips of the fingers of both hands, and by the 20th the palms were affected also; the backs of the hands were normal then, but have become involved since. There was never any sphincter affection at any time. Except for the 'creeping and pricking sensations' there had never been any pain. She had not felt any numbness of the tongue, nor had her speech been affected. She states definitely that she had no headache or backache, no pain or discomfort along the spine, no abdominal or thoracic pain, no 'rope-' or girdle-sensations, or giddiness.

She was first seen by me on May 23rd, when the above history was obtained. Now she says she feels no longer any pricking in her legs, feet, or hands; in fact as regards the hands she only has the feeling of numbness as far as the wrists, but in the feet and legs, in addition to this, she still has the 'creeping and crawling' sensations. For the first three weeks or so of her illness she suffered a good deal from constipation; but lately she has been having two or three loose actions daily and feels better, the numbness and other unpleasant sensations being a little less; she affirms this quite definitely.

The following were the conditions noted when the patient was examined on May 23rd :—No pigmentation of the hands, forearms, face or neck; nothing

suggestive of pellagra. There is a patch over the lower two inches of the radial aspect of the right forearm where the pigment is deficient, and in the centre of this is an old cicatrix. There is no roughening of the skin over the area. This may be the result of an old attack of yaws; she cannot state when she first noticed it and thinks it has always been there. Her mental state was good and she replied readily to all questions.

*Muscular power.* All the ordinary movements are performed with little, if any, diminution of power; there is certainly not more than would be accounted for by the ataxic condition present.

*Sensation.* The changes are mainly subjective, but there is a definite, though slight, alteration observed with the following tests. A wisp of cotton-wool is felt (with the eyes bandaged) all over the area where the patient states she has the numb sensation, but affirms that the feeling of the touch of the wool is 'not the same' as over the normal skin. Pin-head and pin-point are readily perceived and differentiated, and accurately located.

*Heat and cold.* These are distinguished correctly, but there appears to be a little delay in the perception. Thus, touch is replied to immediately, but heat and cold seem to be noticed only after an appreciable interval of two to four seconds.

*Vibration sense.* Is definite and appears to be quite normal.

*Position and Joint sense.* Do not seem to be affected. In one instance, with the right leg bent up and crossed over the left, she stated that the limb was straight, but since on every other occasion the position of the limbs was accurately described I am inclined to think that either she was describing the position of the left leg, or she was not attending, or lastly that she did not grasp the question, for this was in one of the earlier tests of position sense.

There is no pain on ordinary pressure of the muscles, no joint pain, either spontaneous or on movement or on palpation. There is no tremor on extension of the arms and fingers, nor when at rest. The pupils react normally, there is no nystagmus.

There is no hyperaesthesia above the anaesthetic or paraesthetic areas. The cranial nerves are not affected; sight, hearing, taste, all seem to be normal. She can appreciate the difference in thickness between two similar objects, e.g., two note-books, and also weights within 10 grammes of each other. She recognises a pen, a hairpin, a coin, a watch, by sense of touch with eyes shut.

*Ataxia.* When asked to touch the tip of her nose with the tip of her forefinger, or to bring the finger-tips together, all with the eyes closed, she usually missed the contact by a couple of inches or so; there is no intention-tremor. She can follow an object moved in space fairly closely with either hand. She has some difficulty in picking up a pencil between the thumb and first finger of either hand; this difficulty increases with the middle and ring fingers, and she is quite unable to pick it up between the thumb and little finger. With a smaller object, such as a pin, all efforts are ineffectual, she cannot pick it up even with the thumb and forefinger.

As regards the legs: she is quite unable to walk or even to stand unaided. Romberg's test, therefore, cannot be carried out. When she is supported on both sides and an endeavour is made to walk, the legs are thrown wildly about, or they cross over each other, or may double up under her.

When she lies in bed, however, she can, though badly, more or less follow a moving finger with her feet.

*Reflexes.* Deep reflexes are absent. No knee-jerk or Achilles' tendon-jerk elicited, nor the supinator or triceps reflex. The superficial reflexes are present; the plantar somewhat exaggerated. The Babinski reflex was certainly not extensor,

though, as already stated, in a native this is difficult to obtain at all, owing to the thickness of the skin of the sole. In this patient the foot and leg were drawn up sharply, but there was no dorsiflexion of the toes.

The temperature had generally varied between 98° and 99° F., and once touched 100° F., but since the 20th it had been normal. The blood and cerebro-spinal fluid gave a negative Wassermann reaction. The results of the detailed examination of the former will be given at the end of the description of her case. The latter was clear and to all tests normal; cells few, practically all mononuclears, no organisms, bacteria or treponemata found. Albumen not in excess.

The faeces contained ova of ankylostoma.

On June 11th she was examined again; her general condition seemed to be a little improved. She stated that the numbness in hands and wrists was less marked, and this must be taken according to her assertion, for, as shown above, tests with wool, etc., revealed nothing objectively before. The inco-ordination of the upper limbs remained as at previous examination; the condition of the legs was as before. They seemed to be no worse, but there was certainly no improvement. The position-sense was not quite so accurately estimated as on the former occasion; the muscle pressure sense was still unaffected. The stereognostic sense had distinctly deteriorated. With her eyes shut she could not recognize by touch, a key, a pocket-knife, a match-box, a coin, etc., although she readily named them on opening her eyes. Also, as regards weights (as stated above, closely approximating weights were distinguished at the examination on May 23rd), two match-boxes containing the one a 5 gramme weight the other 72 grammes were not distinguished with any accuracy. She usually said the box with 5 grammes was the heavier, or that they both felt the same. When the weights were hung on to the toes or round the ankles she made similar replies. She was still unable to walk or even to stand. The faeces still contained hookworm ova in considerable numbers.

A third examination carried out on June 22nd revealed nothing new. She still affirmed that the numbness of the hands and fingers was diminishing; and now added that, though the feet and legs felt as numbed as before, the tingling had disappeared, but the crawling sensations had not altered. On repeating the same tests as on the two previous occasions no change could be detected. She stated on this occasion that her eyes seemed 'a little dim' and that reading was difficult because the letters ran together.

I regret to say that this patient, showing no further improvement, was taken away from the hospital shortly afterwards.

Blood examination on May 23rd gave the following results:—

Erythrocytes 3,312,000 per c.mm. Occasional nucleated cells seen, some degree of anisocytosis, no noticeable poikilocytosis, staining reactions normal, no malarial parasites.

Haemoglobin 60 per cent. Colour Index 0.9.

White corpuscles 9,300 per c.mm.

Blood examination on June 11th gave:—

Erythrocytes 3,480,000 per c.mm.; none nucleated.

White corpuscles 9,000 per c.mm. Haemoglobin 60 per cent.

Colour Index 0.89.

On the 23rd June the erythrocytes numbered 3,600,000 per c.mm.; Haemoglobin 64 per cent., practically the same as on the previous occasion, giving a colour index of 0.88. Leucocytes 10,100 per c.mm. There is thus an increase

in leucocytes, and, as will be seen, a tendency to a thrust to the left in the Arneth count as the disease continued.

There follows in tabular form the results of the differential leucocyte counts on the three occasions:—

	May 23rd	June 11th	June 23rd
Polymorphonuclears ...	37·8	46·4	49·0 per cent.
Promyelocytes ... ..	0·6	0·8	0·8 „
Myelocytes ... ..	2·0	2·4	1·4 „
Metamyelocytes ... ..	0·8	1·6	1·2 „
Eosinophile Myelocytes	0·4	0·2	— „
Eosinophiles ... ..	10·0	8·4	5·8 „
Basophiles ... ..	1·8	0·8	0·2 „
Large Mononuclears ...	3·4	4·6	4·2 „
Transitionals ... ..	3·4	3·4	2·2 „
Lymphocytes ... ..	39·8	31·4	35·2 „

Arneth counts:—

	I	II	III	IV	V	S
May 23rd	5·8	48·7	31·2	5·3	2·6	6·4
June 11th	8·2	46·1	28·9	7·3	3·5	6·0
June 23rd	11·4	58·0	19·2	2·0	1·6	7·8

Arneth Index:—

May 23rd 71·1; June 11th 68·7; June 23rd 79·0.

(b) C.H., female, aged 36 years. This patient stated that she was quite well until the end of April, 1917. She was doing some washing when quite suddenly she felt an itching in her eyes; the right was first attacked and some three to four hours later the left. She said that her mouth was not sore at any time. The following day there was 'stickiness' of the lids, and the light caused pain. Three days later she felt that her toes were getting numbed and then the soles of her feet. During the succeeding week this feeling gradually extended up to the hips. On or about the 10th May similar numb sensations started in the fingers, but now accompanied by pricking; this extended as far as the wrists but not beyond. She was very constipated throughout. The condition remained practically unchanged for a month, then from about 12 June she thought she had improved a little, but the improvement was very slight.

On examination on June 22nd I have the following notes:—

'Patient is unable to walk at all, or even stand without being supported. There is marked ataxia. There is also a considerable want of co-ordination in the movements of the fingers, but this had improved more than any other symptom apparently, and she is now trying to sew, but finds it very difficult and often drops her needle. She can pick up a pencil between the thumb and first, middle or ring finger, but not the little finger. With the left hand the attempt to do the last is better than the right (the patient is right-handed). She complains now of pains all down the arms, most troublesome at night. On further enquiry into this symptom I am given to understand that this sensation is not that of real pain, but that the arms feel uncomfortable and that she cannot place them in any position in which they are eased sufficiently for her to sleep well. Knee-jerks not elicited; wrist-jerk doubtful. The changes, as in other cases, are practically entirely subjective, no true loss of sensation is detected over the "numb" areas by the usual tests. No ova detected in the faeces.'

A blood examination was made on June 22nd, and gave the following results :—

Polymorphonuclears	...	...	...	...	48.2 per cent.
Promyelocytes	...	...	...	...	0.6 "
Myelocytes	...	...	...	...	1.4 "
Metamyelocytes	...	...	...	...	1.4 "
Eosinophiles	...	...	...	...	3.2 "
Basophiles...	...	...	...	...	1.6 "
Large Mononuclears	...	...	...	...	2.4 "
Transitionals	...	...	...	...	3.2 "
Lymphocytes : large	...	...	...	9.6	
small	...	...	...	24.6	
Türk's	...	...	...	3.4	
Rieder type	...	...	...	0.4	
				—	38.0 "

Arneth count :—

I	II	III	IV	V	S
8.7	46.5	30.3	7.0	4.6	2.9
Arneth Index 70.8.					

It will thus be seen that the stage of the disease corresponds closely to that of the last case when the blood was taken on the third occasion, and the differential count is strikingly similar. The main difference is in the eosinophiles, and this is explicable by the presence of hookworms in the former and their absence from the latter.

6. *Severe case ; result not known, probably fatal.*

A.D., female, aged 25 years. The history obtained from this patient was that on March 1st, 1917, her eyes suddenly 'began to burn.' Previously she had been quite well. A week later her mouth became sore at the corners, but this did not cause any pain or interfere with her taking food. A fortnight after the onset (March 15th) she felt a sensation of 'heat in the soles and tops of the feet,' spreading up gradually till it reached the knees by the 21st. Coincidentally with the extension of the feeling of heat the toes and soles of the feet began to be numb. Up to the 21st she was able to walk, but by the 23rd the numbness had extended to the knees and walking was impossible, owing, as she stated, to 'the knees not being able to bear her.' On the 24th her finger-tips began to feel numb (no sensation of heat here), and the following day the same sensation was spreading over the backs of the hands. On the 27th she stated that her 'face felt tight,' but not numbed at all. She had had plenty of food (mainly sugar-cane) prior to the onset of her illness ; she had been getting good wages and was not starved at all. There had been no vomiting, no fever, and she had been constipated throughout. Three days later she was much worse ; I was told that she had become 'totally paralysed,' but this turned out to mean that, owing to the numbness and inco-ordination when movement was attempted, she lay still ; no actual paralysis could be made out anywhere.

It is a matter of great regret that this case could not be watched through and an autopsy obtained, as the march of events in her case, though following the usual lines as regards the nature of the symptoms, was much more rapid than the average. As she was going downhill, her friends came and took her away at her own request, and subsequent enquiries at the address she gave proved fruitless, and she could not be traced.

Her state on examination on March 25th was as follows :—



She had to be supported on both sides when she was asked to get out of bed ; there was marked ataxia, the legs being quite uncontrollable ; the gait, therefore, could not be tested, nor Romberg's sign. There was no resemblance to the tabetic kick, the legs simply 'flopped about' uncontrolled. Pupils reacted to light and convergence. Knee-jerks not elicited, nor Achilles' tendon reflex, nor the wrist-jerk ; the triceps jerk was obtained. When sensation was tested, cotton-wool, pin-head, pin-point, heat and cold were all correctly recognised and accurately localised everywhere. The only change detected was that perhaps once in seven times heat was described as cold, and that generally the conduction of this sensation appeared to be delayed. Allowance being made for the ataxia, no definite loss of power in the various movements could be detected. There was no involvement of the sphincters. No mental change ; the patient was perfectly rational and replied to all questions clearly and promptly and stated that although even the wisp of cotton-wool was felt, it 'seemed duller' over the numb parts. Vibration-sense apparently normal, but sense of position and joint-sense were defective.

The urine contained some dicalcium phosphate crystals, but nothing else abnormal. Faeces showed ova of ankylostoma and ascaris, but unaccompanied by any eosinophilia.

Blood examination on March 25th, 1917:—

Polymorphonuclears	...	...	...	...	52.8 per cent.
Promyelocytes	...	...	...	...	1.4 "
Myelocytes	...	...	...	...	1.0 "
Metamyelocytes	...	...	...	...	1.0 "
Eosinophiles	...	...	...	...	2.0 "
Basophiles	...	...	...	...	0.6 "
Large Mononuclears	...	...	...	...	2.6 "
Transitionals	...	...	...	...	1.6 "
Lymphocytes : large	...	...	...	7.6	
small	...	...	...	28.2	
Türk's	...	...	...	1.0	
Rieder type	...	...	...	0.2	
				—	37.0 "

Arneth count :—

I	II	III	IV	V	S
10.3	42.0	29.9	11.0	3.4	3.4

Arneth Index 67.2.

While doing the count a few erythroblasts were seen, some with bizarre-shaped nuclei ; some degree of chromatophilia, and two corpuscles showed basophilic stippling.

#### 7. *Severe cases terminating fatally.*

(a) J.P., male, aged 25 years. History : The illness began on March 3rd with 'burning in the eyes' followed after an interval, the duration of which is not remembered, by 'sore mouth.' On March 17th his feet felt numb and walking became difficult. During the succeeding three or four days the numbness extended up the legs and the 'knees felt hot,' but were not painful. The symptoms of numbness and heat have been slowly getting worse. When seen on March 28th the eyes were suffused, and the lids exuded a little pus ; also there was some, not very marked, degree of photophobia. There were some

shallow ulcers, more of the nature of superficial abrasions, along the edges of the lips. Knee-jerks could not be elicited; gait showed little if anything abnormal, there was a tendency to lift the feet higher than normal, suggesting the steppage gait. Pupils reacted normally; Romberg's sign not present. No loss of power could be detected, nor, objectively, any alteration of sensation. No muscle-pain, the vibration-sense not affected, and weights readily differentiated.

Some pus was taken from the eye, and also smears from the surface and edges of the abrasions on the lips. Cultures on various media both aerobically and anaerobically revealed nothing abnormal; the various colonies which grew were examined, and only the usual air and mouth-organisms were found. No cell-inclusions could be discovered after prolonged search. The faeces contained ova of *ankylostoma*; urine normal.

On April 12th the condition was worse; he was by this time quite unable to walk, and his fingers, hands, and wrists felt numbed. His speech was inclined to be blurred, and he stated that his tongue 'felt heavy.' All tongue movements carried out normally, no sign of any atrophy of tongue muscles, or of any other muscles. Taste normal, but weights as wide apart as 10 and 70 grammes not differentiated with any accuracy. Joint and position-senses also affected. He did not move in bed owing to the numbness, but when asked to move he could do so normally though slowly, and there was no sign of actual paralysis anywhere. Quoting from my notes on this date:—He is becoming emaciated and does not take his food well. He states that he has no appetite, but he can swallow without any difficulty; there is no change in his voice. He has been very constipated from the beginning of his illness.

He remained in the condition described above, except that he became generally weaker. On April 20th diarrhoea set in, and he had an average of eight loose watery actions daily. He lay quite helpless and passed all motions under him, but not strictly involuntarily; that is, he felt the desire, but the motion passed before the nurse could come and attend to him. The diarrhoea continued until the 25th when death occurred at 3.15 a.m. A post-mortem examination was performed the same day. Cultivation of the faeces during the last few days revealed nothing abnormal, with the exception of a chromogenic organism giving the following reactions:—

Markedly motile, rendering milk alkaline, but without the production of any clot; producing acid but no gas in the following media: lactose, saccharose, dulcite, mannite, glucose, maltose, and dextrin. Examination of the blood was carried out on three occasions, namely, on March 28th, April 12th and 18th.

March 28th:—

Erythrocytes 4,200,000 per c.mm.; two nucleated red cells seen, no malarial parasites detected.

White cells 8,600 per c.mm.; Haemoglobin 80 per cent.

Colour index 0.85.

April 12th:—

Erythrocytes 3,800,000 per c.mm.; no nucleated corpuscles seen.

White cells 9,600 per c.mm.

Haemoglobin 72 per cent. Colour index 0.95.

April 18th:—

Erythrocytes 3,600,000 per c.mm.

White cells 11,200 per c.mm.

Haemoglobin 62 per cent. Colour index 0.86.

Differential leucocyte counts on these three occasions :—

	March 23rd	April 12th	April 18th	
Polymorphonuclears ...	45.0	41.0	64.0	per cent.
Promyelocytes ...	0.4	0.6	1.0	„
Myelocytes ...	0.6	1.4	1.2	„
Metamyelocytes ...	1.0	0.2	—	„
Eosinophile myelocytes ...	—	0.4	—	„
Eosinophiles ...	4.0	7.2	6.8	„
Basophiles ...	0.6	0.8	1.0	„
Large Mononuclears ...	2.6	2.2	3.2	„
Transitionals ...	2.2	1.8	2.6	„
Lymphocytes—				
large ...	7.4	5.4	3.2	
small ...	35.2	35.8	14.6	
Türk's ...	1.0	2.8	2.2	
Rieder	—	0.4	0.2	
Arneth count :—	43.6	44.4	20.2	„

	I	II	III	IV	V	S
Mar. 23rd	4.5	33.8	40.0	12.5	5.4	3.8
Apr. 12th	6.8	36.6	36.1	12.7	3.4	4.4
Apr. 18th	6.6	43.1	30.6	9.7	6.9	3.1

Arneth Index :—

March 23rd 58.3 ; April 12th 61.4 ; April 18th 65.0.

It will thus be seen that as the patient got worse the polynucleosis increased and the lymphocytes decreased, and the Arneth count shifted more and more to the left ; although the final differential count shortly before death gave practically a normal percentage.

The cerebro-spinal fluid was taken by lumbar puncture, smears and cultures put up, but no growth occurred on any of the media employed, and nothing abnormal was detected in the smears.

At the post-mortem examination the following points were noted :—

The body was emaciated, the subcutaneous fat was only small in amount, but the muscles did not appear to be much wasted and were of a good colour. Spinal fluid was taken again, was clear and limpid, and flowed slowly, drop by drop from the lumbar puncture (cultural attempts proved sterile as on the former occasion).

*Spinal cord.* Vessels not injected, except a little perhaps over the lumbar region. There was no meningitis, nor did the cord itself appear softer than normal on section.

*Brain.* No inflammation of the meninges ; there was a faint serous haze over the vertex ; nothing else noticeable. There was very little fluid in the ventricles, and the brain tissue appeared normal on section.

*Thorax.* Practically no subcutaneous fat. There were firm pleural adhesions on both sides, more on the right and firmest there, especially over the upper lobes ; no fluid in the pleural cavities. No sign of any tuberculosis. The upper and middle lobes of the right lung were firmly bound together by adhesions, in fact they could not be separated without dissection. The lung tissue was crepitant all over.

*Heart.* Pericardium contained 10 to 15 c.c. of pale, straw-coloured fluid. There was a slight atheroma at the base of the aorta ; nothing else abnormal, valves competent.

*Abdomen.* Nothing abnormal seen, no free fluid, no signs of any peritonitis; stomach normal.

*Spleen.* A little enlarged, with slight local perisplenitis, tissue macroscopically normal.

*Liver and kidneys.* Normal.

*Mesenteric glands.* Enlarged and pink.

*Small Intestine.* Contained three ascarides. The contents otherwise consisted of a greenish material, no blood. The vessels were congested over the lower six feet or so, but not markedly till about two feet above the ileo-caecal valve, when the congestion became deep and there were small ulcerous patches with denudation of the mucous membrane (resembling a dysenteric condition) but the surface was pale, not injected. Here and there were small pigmented patches varying from one to four centimetres in diameter. Peyer's patches apparently normal.

*Large Intestine.* Congested and showed small denuded areas, mainly in the ascending colon and the hepatic flexure.

The following tissues were taken for further microscopic examination: Brain cortex, cerebellum, pons, medulla, basal nuclei, olfactory lobe, optic nerve, roots of the various cranial nerves; cervical cord at three different levels, dorsal and lumbar cord at three levels, lumbo-sacral cord; sciatic, median, and ulnar nerves; skeletal muscles, heart muscles, tongue muscle, lung, thyroid; liver, spleen, kidney, adrenals, stomach mucous membrane, intestine, and pancreas.

These were treated in various ways and will be spoken of presently, as the findings were practically identical in this and the case next to be described, and one description of the microscopical findings will suffice.

(b) G.P., male, aged 36 years. The history obtained from this patient was that he was quite well until Feb. 20th. During that day his right eye started to 'itch and burn,' and within a few hours the left was similarly affected and the light caused pain. He had been earning good wages and stated that he had had plenty to eat, though the food consisted largely of sugar-cane. On the third day of the illness (Feb. 22nd) his mouth became sore and for 24 hours or so he could not eat on account of the soreness; after the first day of this, however, he was able to take food with little or no discomfort. No further symptoms declared themselves until the beginning of March, the 2nd or 3rd, when he began to feel a numbness in the toes and soles of the feet; this gradually extended over the dorsa and up the legs, till by the 14th he had considerable difficulty in getting about. The difficulty increased, and by the 20th walking became impossible. Four days later he began to feel a similar numbness, with some tingling in the finger-tips of both hands. He had been obstinately constipated from the start.

When examined on March 28th he was lying in bed; he was not paralysed, but on attempting to get up, the ataxia was extreme, the legs being thrown wildly about; the arms were partially ataxic also. Deep reflexes (knee-jerk, ankle-jerk) not obtained in the legs, nor the wrist-jerk in the upper extremity; the triceps was doubtful. Testing the various movements of arms and legs revealed the fact that there was very little, if any, loss of power; but the joint and position senses were defective. As regards sensation nothing could be detected objectively except some confusion between heat and cold. Although no defect in perception of sensation to touch, pin-point, etc., could be made out to the observer, the patient stated that the feeling to him was 'different' over the areas described as numbed, saying that the sensation was 'duller.' His talking was a little thick and he stated that the tip of his tongue felt 'heavy'; sibilants were badly

pronounced. No paresis of the tongue muscles could be made out, and no alteration in the sense of taste. The mouth was sore and appeared inflamed; there were ulcers at the angles of the mouth and a few aphthae on the mucous membrane of the lips. The eyes showed superficial abraded areas on the lids at the margins, and there was a purulent discharge from the conjunctiva. Smears from the eye pus showed nothing particular, no inclusions detected, and on culture merely the usual organisms grew, mainly staphylococcus albus and micrococcus catarrhalis. In smears from the mouth and its ulcers no inclusions were seen, and on cultivation staphylococci, streptococci, etc., developed, nothing distinctive. Faeces contained no helminth ova, and though constipated, appeared otherwise normal. Urine normal.

When seen again on April 12th he was much worse. I have in my notes on that day:—“He talks badly because, as he puts it, his “tongue is heavy and numbed”; there is still, however, no paresis; all the movements are carried out normally, and there is no atrophy. He only takes soup and soft food, he lies in bed without moving, but can move when he wishes. He states that he has “tingling in the face now.”

On April 15th when moving about in bed he fell off, and as he was restless a bed was made up for him on the floor. On the 18th profuse diarrhoea came on, 15 to 20 actions daily, and death occurred on the 20th. The mind was apparently quite clear till the last. Cerebro-spinal fluid had been taken, but examination of smears revealed nothing abnormal, the cellular elements were not increased, the fluid was clear and flowed drop by drop, and was not under pressure. The fluid gave a negative Wassermann reaction.

Blood examinations were made on March 28th and on April 12th. A few of the red cells showed some stippling, and others showed polychromasia, but these were few; no nucleated red corpuscles were seen, nor any parasites. No inclusions of any sort in the leucocytes. Differential counts of the latter gave the following results on the 28th of March and the 12th of April respectively:—

	Mar. 28th	Apr. 12th
Polymorphonuclears ... ..	47·8	67·0 per cent.
Promyelocytes ... ..	0·2	0·2 „
Myelocytes ... ..	0·2	0·8 „
Metamyelocytes ... ..	0·8	— „
Eosinophiles ... ..	1·4	2·0 „
Basophiles ... ..	0·4	1·0 „
Large Mononuclears ... ..	3·2	3·4 „
Transitionals ... ..	3·6	1·2 „
Lymphocytes: large ... ..	9·6	4·6
small ... ..	28·8	17·8
Türk's ... ..	2·6	2·0
Rieder ... ..	1·4	—

Arneth count:—  
 ——— 42·4      ——— 24·4

	I	II	III	IV	V	S
Mar. 28th	5·4	38·5	35·6	12·9	5·5	2·1
Apr. 12th	7·7	43·0	33·4	9·6	4·8	1·5

Arneth Index:—

March 28th 61·7; April 12th 67·4.

It will thus be noticed here again how the differential count shortly before death approached the normal percentages, and the actual figures correspond remarkably closely with those of the last case, J.P.

At the post-mortem examination on this patient the following conditions were found macroscopically :—

Body emaciated ; no sign of any rash, either pellagrous or of any other condition. The loss of subcutaneous fat in this case also was very marked, the muscles were small but of good colour. Before undertaking any dissection of the body a lumbar puncture was performed. The fluid was clear and flowed readily, but not under increased pressure. Smears were made but revealed nothing abnormal, and cultural attempts on various media proved sterile as before.

*Nervous system :—*

*Spinal cord.* No sign of any inflammation of the meninges, and no haemorrhages. The veins were congested, especially over the dorsal and upper part of the lumbar regions. The posterior part of the cord appeared softer than normal on section.

*Brain.* No sign of meningitis present ; the vessels of the surface were somewhat congested but not markedly so ; the ventricles did not contain any excess of fluid.

*Thorax.* No pleural adhesions, and no fluid in the pleural cavities. The trachea contained a little yellowish, frothy mucus. The veins below the epiglottis appeared prominent. The tongue was covered with white fur which was easily removed ; there was no atrophy of the tongue or wrinkling of the surface.

*Lungs.* Left upper lobe was of a brick-red colour and congested, but crepitant all over and floated readily in water ; the right showed a similar congestion and coloration in the upper and part of the lower lobes, the middle did not appear to be affected. There were no signs of any tuberculosis.

*Heart.* Except for slight atheromatous patches at the root of the aorta, nothing abnormal was detected. The valves were all competent.

*Abdomen —*

*Liver.* This organ showed puckered areas over the right lobe, and on section the tissue appeared somewhat darker than normal and showed a similar cicatrix ; nothing resembling ordinary gummata.

*Spleen.* Capsule thickened ; tissue dark but of normal consistence ; organ not enlarged.

*Kidneys.* Apparently normal.

*Stomach.* Contained about half a pint of greenish watery fluid and grumous mucoid material of the same colour ; the mucous membrane was to all appearances normal.

*Small Intestine.* Mucous membrane normal till the lower three or four feet were reached, when the vessels became prominent and increasingly so down to the ileo-caecal valve, when the congestion became acute. Scattered at intervals were some half a dozen dark, pigmented patches, visible also from the serous surface. Peyer's patches were not unduly prominent ; solitary follicles clearly defined.

*Large Intestine.* Mucous lining pink, but congestion by no means marked.

*Mesenteric glands.* Slightly enlarged.

The results of the microscopical examination will be detailed after the other cases have been described. The same tissues were taken as from the last patient.

(c) T.J., male, aged 28 years. Both the onset of the symptoms and the course of the disease were slower in this patient than in any of those previously recorded. The history given by this patient was that until March 1st he had been quite well. On that date his right eye began suddenly to itch and became red ; two days later the left was similarly attacked ; on the 15th (a considerably longer interval than in the last case) the mouth became affected ; it felt sore and hot

so that he was unable to take his food for 24 hours. After this he could eat without pain. His feet began to feel numbed on the 20th or 21st, and this condition spread upwards so that on presenting himself at the hospital on the 23rd, though he was able to walk, he had not complete control over his legs. He had been very constipated from the onset of his illness.

¶ Examined by me on March 28th when the following notes were made :— 'Eyes not very inflamed now, but a viscid purulent discharge is present, and there are shallow abrasions at the edges of the lids and on the palpebral conjunctiva. The mouth is sore; there are ulcers at the angles and shallow aphthae on the mucous membrane of the lips. The tongue is not affected. He is able to walk, but, when getting out of bed, the legs are thrown about; the gait is ataxic but not stamping; he can turn without stumbling; knee-jerks are absent; to the Babinski test there is no response. He states that there is "numbness up to the knees," but objectively no alteration of sensation can be detected, though the patient states that "touch feels different" over the area from the knees downwards. As far as can be tested Romberg's sign is not present. Pupils react normally both to light and convergence. The faeces contain ova of ankylostoma and ascaris.'

He was examined again on April 12th when his condition was found to be considerably worse. He was unable to walk, and when supported on both sides in attempts to walk, the legs were quite uncontrollable and were thrown about in all directions, sometimes spread wide, at other times catching in each other. 'He complains now (April 12th) of tingling and numbness in the fingers and of "pain" in the upper arms; no pain at all in the joints. Both hands were affected together and the sensation is spreading upwards daily. The tongue feels numb at the tip and his speech is altering, owing, as he states, to a "heavy feeling in the tongue," and there is obvious difficulty in pronunciation of certain words, especially those containing sibilants. He is quite rational and answers all questions readily, promptly and intelligently.'

When seen again on April 25th he was totally unable to walk, even when supported by an attendant on each side. 'Talking is difficult, so he rarely speaks, but when addressed he answers rationally as before. He is clearly going from bad to worse.' Position and joint senses considerably affected, apparently, but his dysarthria makes accurate estimation very difficult. Cerebro-spinal fluid was taken on this occasion; it flowed readily, but was quite clear and limpid; nothing abnormal was detected in smears made of the fluid as it flowed, and also after prolonged centrifugalisation; there was no deposit. Cultural attempts all remained sterile, and the Wassermann reaction carried out with this fluid and with the blood was negative in each case.

The patient remained in this condition for nearly three months without any further spread of the numbness and, in fact, without development of any fresh symptoms except that he was becoming gradually weaker and weaker. During this time the bowels were opened naturally about once a day, occasionally twice and sometimes only on alternate days; the stools were natural. On July 19th, however, diarrhoea began to set in, five or six actions occurring daily, increasing to ten, and the patient died three days later. When seen on the 19th, though he did not move voluntarily, but lay quiet in bed, there was no real paralysis detected; movements of the limbs, though weak, were all carried out normally; tongue not affected as regards its movements.

Blood examination was carried out on April 12th and again on July 19th.

I regret to say that I cannot find the records of the total counts, but the differential leucocyte counts on these dates were as follows:—

	April 12th	July 19th
Polymorphonuclears ... ..	49.8	54.6 per cent.
Promyelocytes ... ..	0.2	0.8 „
Myelocytes ... ..	0.4	0.6 „
Metamyelocytes ... ..	0.8	1.0 „
Eosinophiles ... ..	3.0	4.8 „
Basophiles ... ..	1.2	1.4 „
Large Mononuclears ... ..	2.0	2.4 „
Transitionals ... ..	2.0	2.2 „
Lymphocytes: large ... ..	6.2	5.0
small ... ..	32.2	25.0
Türk's ... ..	1.8	1.2
Rieder type ... ..	0.4	1.0
	— 40.6	— 32.2 „

Arneth counts:—

	I	II	III	IV	V	S
April 12th	8.4	53.4	24.6	8.4	2.4	2.8
July 19th	8.7	54.6	23.9	8.1	1.8	2.9

Arneth Index:—

April 12th 74.1; July 19th 75.2.

(d) M.H., female, aged 30 years. This case ran a more prolonged course than the first one recorded in this series, but less than the last, the total duration being about two months. The history of this patient is somewhat vague; her statements as to the chronological order of the events were not altogether consistent. At one time she stated that the numbness was the first symptom, but patient enquiry elicited that the course was probably as follows:—

On or about March 12th her eyes and mouth became 'sore and itched'; she could not remember which was affected first; eight days later she felt a 'tightness of the chest' or, as she sometimes described it, 'a rope feeling' there. At the end of the month (28th or 29th) her toes and the soles of her feet felt numbed, and this sensation extended to the knees and interfered more and more with her walking.

When seen by me on April 12th she was totally unable to walk and could not even get out of bed. The knee-jerks were exaggerated and multiple, patellar and ankle clonus were marked. This had been the only case so far of those recorded in which the reflexes were increased. The sensory alterations were subjective only, as in the other patients. In the upper limbs the reflexes were normal. Pupil reactions normal; no inflammation of the eyes or mouth now, no affection of speech, and no tremor, either volitional or when at rest.

Her blood was taken on this date and gave a negative Wassermann reaction; the blood count was very similar to that of G.P. [No. (b) of this series] towards the end of his illness, except that the percentage of large mononuclears and transitionals is higher; the differential leucocyte count gave the following results:—



Polymorphonuclears	...	...	...	...	60.4 per cent.
Promyelocytes	...	...	...	...	0.2 "
Myelocytes	...	...	...	...	0.6 "
Metamyelocytes	...	...	...	...	0.2 "
Eosinophiles	...	...	...	...	3.2 "
Basophiles	...	...	...	...	1.2 "
Large Mononuclears	...	...	...	...	5.8 "
Transitionals	...	...	...	...	3.0 "
Lymphocytes : large	...	...	...	...	6.6
small	...	...	...	...	17.8
Türk's	...	...	...	...	0.4
Rieder type	...	...	...	...	0.6
				—	25.4 "

Arneth count :—

I	II	III	IV	V	S
8.9	46.4	27.5	11.3	3.3	2.6

Arneth Index 69.0.

Her further history showed that the symptoms took on the character of the cases already described ; thus, the reflexes soon disappeared, the condition of numbness extended to involve the hands, and later the tongue. Her temperature on admission to hospital was 100° F., but thereafter, with one exception when 99° F was recorded, was normal. She suffered from constipation until the 7th of May when the actions became looser, and diarrhoea set in, and the case terminated fatally on May 14th.

(e) J.M., male, aged 28 years ; the husband of the patient, E.M., whose case has already been described. J.M. was admitted to hospital on April 19th when the history obtained from him was that towards the latter part of February his eyes became sore and inflamed, 'they itched and were red.' Some time later (he could not state definitely how long was the interval) his mouth also became sore. After this no further symptoms declared themselves, except for troublesome constipation, until March 28th when he felt a 'numbness' in the feet—the toes and soles—which in the course of a few days extended to the level of the knees. He never felt any 'fever.'

When seen on April 12th his lids showed abraded areas, and there was a mucopurulent secretion present ; the mouth was ulcerated at the angles and fissured ; the mucous membrane of the lips was inflamed, but he was able to take food without pain. He was unable to walk without help ; when supported he had an ataxic gait, and suggestive of spasm, but not tabetic ; he was not able to stand alone, so Romberg's sign could not be tested. Tactile sense appeared normal with the usual tests, though the patient himself stated that he could perceive the difference over the areas complained of as being numb. Sensation of heat and cold, joint, and vibration senses apparently normal. Knee-jerks absent. Allowing as far as possible for the ataxia there was no detectable loss of power in the leg movements. Hand and arm movements normal ; grip good.

On April 25th the blood was taken for a Wassermann reaction and the cerebro-spinal fluid for the same test ; smears and cultures were also made with the latter. Nothing abnormal was detected, and the culture tubes remained sterile. The Wassermann reaction was quite negative with both the blood and the cerebro-spinal fluid. I have the following note on that day (April 25th).—'Patient about

the same, no improvement, but no further extension. The numbness reaches just to the thighs, but neither the hands nor the tongue are affected at all. He is no longer constipated, but the bowels are acting normally, as a rule once daily, occasionally twice.

His condition remained practically unchanged for nearly four weeks after this, when on May 21st diarrhoea set in. There was no further spread of the nervous symptoms except that defective estimation of joint and position senses ensued; his replies to questions as to relative weights were too variable for certain record. He appeared to guess rather than to reply intelligently, but there was almost certainly some defect in the power of estimating weight differences. The number of actions of the bowels on the 22nd, 23rd, 24th and 25th, was six, four, six and fourteen respectively. The temperature which had been normal ever since his admission to hospital, rose slightly to 99.2° F. on the 26th May, on which day the patient died.

I am unable to find my notes of the blood examination of this patient, except the record of the Wassermann reaction.

It is worthy of note in this case that he suffered from constipation from the onset and while the nervous symptoms were developing; that when these latter came to a standstill the bowels acted normally, and towards the end, as in the other cases, diarrhoea either led to death from exhaustion or at least was closely associated with the fatal issue.

8. Lastly a brief description will be given of two cases which did not arise at Spanish Town, but which were sent to me by a practitioner in Kingston who had heard of the symptoms presented by the patients at the former place. His remark in sending them was to the effect that the patients were examples of what had been called 'peripheral neuritis' in Jamaica for many years, and he added in each case: 'Is this anything like those seen in the Spanish Town epidemic?'

The first one closely resembles the condition already noted, except that the course was much slower and the knee-jerks were exaggerated; the second differs in that the knee-jerks were present and the disease, so far as the patient could recollect, was not ushered in by eye or mouth symptoms. Thus they correspond somewhat with the case M.H., described above, in which at one stage a similar state of the reflexes was found, though later on they were lost. The patients left for the country parts the day after my examination, and I have not been able to hear anything about either of them since. Possibly in their cases, as time went on, the same disappearance of reflexes may have occurred, but this is uncertain.

(a) J.N., male, aged 24 years. This patient stated that in December 1916 his eyes 'became sore'; there was no photophobia, but there was a slight discharge and the lids were gummed together in the morning on waking. Three weeks later the mouth became affected, being sore particularly at the corners; the condition, however, never interfered with his taking food. One week subsequent to this, or four weeks after the onset, the toes and soles of the feet felt numb. This numbness gradually extended over the dorsum of each foot and up the legs; when seen on April 26th it extended above the hips. Early in February the finger-tips felt numbed, and by the time that I saw him (April 26th) the backs of the hands were similarly affected. There was no numbness of the tongue.

When examined on the 26th April the gait was suggestive of a spastic condition, but not markedly so, rather of a steppage type. The patient stated that the ground felt 'springy' and as if he were "walking on indiarubber." The knee-jerks were exaggerated, and there was a suggestion of ankle-clonus; Babinski's

test gave possibly a slight extensor response, but the skin of the soles was very hard and thick so this point could not be determined satisfactorily. No Romberg's sign present, no nystagmus, no Argyll-Robertson pupil; no loss of power detected. No sensory defects made out objectively, no affection of sphincters. Patient had suffered with constipation throughout.

Blood examination on April 26th gave the following results:—

Erythrocytes 4,400,000 per c.mm.; Haemoglobin 76 per cent.; Colour Index 0.86. No nucleated red cells seen, no malarial parasites found, no poikilocytosis, but some degree of anisocytosis.

Leucocytes 8,700 per c.mm.; differential count gave:—

Polymorphonuclears	...	...	...	41.6 per cent.
Promyelocytes	...	...	...	0.6 "
Myelocytes	...	...	...	1.8 "
Metamyelocytes	...	...	...	0.4 "
Eosinophiles	...	...	...	1.6 "
Basophiles	...	...	...	2.0 "
Large Mononuclears	...	...	...	4.4 "
Transitionals	...	...	...	2.2 "
Lymphocytes: large	...	...	10.8	
small	...	...	32.8	
Türk's	...	...	1.0	
Rieder type	...	...	0.8	

— 45.4 "

Arneth count:—

I	II	III	IV	V	S
6.3	35.1	32.7	14.0	6.3	5.6

Arneth Index 57.7.

The Wassermann reaction carried out with the serum from this patient was negative.

(b) S.C.T., male, aged 36 years. This patient states that his previous health has always been good with the exception of an attack of 'lumbago' in 1912. He cannot say how long the attack lasted, but knows that it 'quite cleared up in a comparatively short time.' Since then he has remained perfectly well until December 1916, when he first began to feel a numbness in the toes and fingers. 'He thinks that the fingers were first affected, but is not sure. The change of sensation at the beginning was very slight indeed, and the feet and hands were affected so closely together that he does not remember the order of involvement.' Since that time walking had become increasingly difficult, so that when I saw him on April 3rd he dared not venture without the aid of a stick, and he stated that he found that at home he walked better and more steadily when holding a chair. When demonstrating this to me he held the chair in front of him off the ground, not in any way as a support, but, as he put it, 'to balance himself.' His complaint at that date was not of numbness but of 'weakness' in the legs and hands. The weakness, however, must have been very slight, for the chair which he used was a comparatively heavy one of mahogany, and he held it out by the top rail in front of him, as already stated. There had never been any tingling or pricking sensation.

At the examination of this patient on April 3rd the following notes were made in addition to the points given above:—

'No apparent affection of the auditory nerves, reacted normally to all the usual tests, watch, tuning-fork, etc., no nystagmus, no diminution of the field of vision, no ocular paresis. Romberg's sign not present; he stands quite steadily with eyes closed, but states that when washing his face he usually steadies himself with one hand on the wash-stand. Knee-jerks present, possibly a little exaggerated, but not brisk or multiple, and there is neither patellar nor ankle clonus. Babinski doubtful, skin thick. Gait is suggestive of spasm, but very slightly. No affection of sphincters. Touch is plainly felt and accurately located everywhere. Joint and vibration senses normal, also sense of position. Heat and cold less certain, six times out of ten he described the hot tube as cold. There is no loss of power in any of the movements beyond what might be ascribed to his not using his leg muscles much of late. The legs are thin; but muscles are not flabby, and electrical reactions are normal. Measurements on the two sides are equal. No tremor of fingers or lips, and there is no affection of speech. The grasp is firm and strong, although he complains of "weakness" in his hands. He says that the ground does not feel soft or woolly, but that he has a sensation as if the floor were "slipping from under him." There is no pain anywhere but a feeling of "weakness" in the knees. In spite of the numbness or weakness of his fingers he unlaced and laced up his boots fairly rapidly and without any difficulty or fumbling. He denies all venereal disease, and there is no evidence of any such.'

The Wassermann reaction was quite negative. A differential leucocyte count gave the following results:—

Polymorphonuclears	...	...	...	...	37.6 per cent.
Promyelocytes	...	...	...	...	0.8 "
Myelocytes	...	...	...	...	0.4 "
Metamyelocytes	...	...	...	...	0.2 "
Eosinophile Myelocytes	...	...	...	...	0.2 "
Eosinophiles	...	...	...	...	10.0 "
Basophiles	...	...	...	...	2.2 "
Large Mononuclears	...	...	...	...	3.0 "
Transitionals	...	...	...	...	4.2 "
Lymphocytes: large	...	...	...	12.0	
small	...	...	...	26.6	
Türk's	...	...	...	1.8	
Rieder type	...	...	...	1.0	
					— 41.4 "

Arneth count:—

I	II	III	IV	V	S
2.7	26.1	34.0	25.0	5.3	6.9

Arneth Index 45.8.

No malarial parasites were seen; no specimen of faeces was obtainable for examination for ova of ankylostome or other worms to account for the eosinophilia. They are present in so large a percentage of natives here that it is more than probable that these cells may be thus accounted for. Far higher numbers may be met with in patients harbouring these parasites here (I recently saw one with 37 per cent.), although there are no obvious indications of helminthiasis in the general state of health, no anaemia, no oedema, shortness of breath, and so forth.

#### IV. SUMMARY OF EXAMINATION OF THE BLOOD

The Wassermann reaction was carried out with the blood of ten of these patients, and in several instances with the cerebro-spinal fluid also, but in every case with negative results. This was done for two reasons: firstly, because it was a natural surmise that patients showing these peculiar nervous symptoms might be syphilitic; secondly, because the suggestion has been made that so-called peripheral neuritis, which is comparatively common here and which so markedly resembles the chronic stage of the condition under consideration, may be sequel to yaws or a 'paraframboesial' affection analogous to tabes dorsalis as a form of parasyphilis.

The results of the Wassermann tests may be summed up in the one word 'negative.' In no instance was a positive result obtained with either the blood-serum or the cerebro-spinal fluid. The tests were performed with every care; standardization is made of the haemolysin, the complement, and the antigen in this laboratory every week when Wassermann reactions are carried out, and the above sera and fluids were tested at the time the routine tests were done, from patients in the hospital and from outside, so that there were abundant controls.

The uniformly negative results dispose of the idea that syphilis is at the root of this peculiar disease.

Passing on to the other blood examinations, it will be seen that total blood-counts were made on eight occasions and differential leucocyte estimations on twenty-eight.

Dealing first with the erythrocyte counts and the haemoglobin percentages, the results in all the cases bore a remarkable resemblance to each other. Thus, in D. J., a mild case of the intestinal form with recovery, there was a 22 per cent. reduction of red cells and a 30 per cent. reduction of haemoglobin, giving a colour index of 0·89; comparing this with E. G., a severe and chronic case of the nervous form, at the stage prior to the acme, there was a reduction of red cells of 34 per cent. and of haemoglobin 40 per cent., giving a colour index of 0·9; at a later examination of this last case, at the height of the disease, when the nervous symptoms were at their worst but the general condition was fair, there was a reduction of 31 per cent. in the red cells and a 40 per cent. in the haemoglobin,

giving a colour index of 0·89; while yet again, when the condition had become chronic, but the general health was still maintained, there had been a little improvement in the erythrocyte count, the reduction being 28 per cent., and the haemoglobin had improved 4 per cent., so that the colour index was 0·88. The difference between these is so slight as to be almost negligible. The condition found in a severe and chronic case, which, however, terminated fatally, showed that there was a gradual reduction in both red cells and in haemoglobin, but not very marked; in fact, when this patient was at the last stages the findings were very nearly identical with those just given in the case of E. G., where the condition was becoming chronic and the general health was fair.

In this case of J. P., when he was in an early stage, up and about, the red cells were 4,200,000 per c.mm., and the haemoglobin 80 per cent., giving a colour index of 0·95; when he was bedridden, and the symptoms were widespread, there had been a further reduction of corpuscles of only 8 per cent. and similarly of haemoglobin, so that the colour index remained the same. Lastly, shortly before death, a third estimation showed only a 4 per cent. further reduction of red cells, with haemoglobin 62 per cent., giving a colour index of 0·86.

Finally, in the case of J. N. (if this be regarded as belonging to the same category, but of a very chronic course), when his general health was good and he was up and about, the colour index was the same as that in the last patient when in extremis, the red cells being 4,400,000 and the haemoglobin 76 per cent.

Practically the only inference one can draw from the above is that the blood condition, as regards the erythrocytes and their haemoglobin content, depends rather upon the general state of health than upon the degree and extent of the symptoms accompanying it.

Comparing the total leucocyte counts in the same patients, it will be seen that the average departs very little from the normal. The mild case of D. J. had 8,400 leucocytes per c.mm.; the very chronic case in a good state of general health, J. N., 8,700. In the severe chronic case, E. G., there was a slight reduction from 9,200 in the earlier stage to 9,000 at the height of the affection, and an increase to 10,100 when the chronic state was fully established, but the general health was fair.

Reviewing the findings in the severe and fatal case of J. P., we see that at an early stage the leucocytes numbered 8,600 per c.mm.; when he was much worse, bedridden and helpless, the leucocytes had increased by 1,000 per c.mm., while the red cells had increased somewhat, and again at the termination of his illness, they had further risen to 11,200, which was only 1,100 more than E. G. when in fair health. The total counts are, therefore, not definite enough to warrant any conclusions as to the cause of the disease or its mode of action, nor do they afford any reliable indications on which to base a prognosis or estimate the stage of the disease.

Passing on to the differential leucocyte count: the accompanying table (Table I) gives the detailed results in percentages. For the estimation of the leucocytes in no case was less than five hundred counted, and in some instances seven hundred to one thousand; while for the Arneth count also at least five hundred were noted. This, as will be readily understood, was a laborious and somewhat tedious undertaking, all the more disappointing in view of the barrenness of inferences to be drawn from it. Each patient appeared to be, as it were, a law unto himself. No sooner did one seem to observe changes in a definite direction in the course of a case, such as, for example, an increase in polymorphonuclears and diminution in the high lymphocytosis, than another analogous case would be met with where none of these changes could be found.

As regards the polymorphonuclears, it is perhaps worthy of remark that the only cases in which the relative proportion of these cells approached the normal, namely Nos. 21 and 23, in the table, were in fatal cases towards the end where the patients were practically in extremis. On the other hand, those who showed the greatest departures from the normal, namely No. 7 with only 27·2 per cent., No. 13 with 30·6 per cent., No. 9 with 33·8 per cent., and so forth, were patients who were not seriously ill or who were recovering.

At the same time it must not be forgotten that in every instance there was found a small proportion of immature forms—promyelocytes, myelocytes and metamyelocytes.

Eosinophilia only occurred in patients whose faeces contained ankylostomes, either alone or with other helminth ova (but see remark on the patient S. C. T., page 142), and in all who had eosinophile

myelocytes, ova were present. One patient, A. D. (No. 18), was harbouring both ankylostomes and ascaris, and yet showed no increase in eosinophiles. A slight relative basophilia was noticed in the majority of cases. The significance of this is doubtful, but it is interesting to note that this condition has been recorded in patients convalescing from beri-beri. Basophilia, however, is not an uncommon condition here; I do not know whether it has been noted in other tropical countries, but I have counted as high a proportion as 5 and even 8 per cent. in the blood of a person in apparently perfect health.

The large mononuclears and transitional cells were increased in a few patients only, and in them not to a great degree. The highest found was 11·2 per cent. in A. B., and she also showed malarial parasites in her blood; with this exception, the highest reached 8·8 per cent. (No. 26) at the height of her illness, which terminated fatally. The average of all those recorded amounts only to 5·9 per cent., or, if the malarial ones be excluded, to 5·7 per cent., in other words, within the limits of the normal. The lymphocytes were increased relatively in all cases except those already mentioned when speaking of the polymorphonuclears, in which the patients towards the termination of their illness showed a differential count closely approaching the normal. Not only was there this lymphocytosis present in all the others, but also in every case there were present the abnormal forms (abnormal, that is, in their entrance into the general circulation) of the Türk's irritation cell and the Rieder type.

Lastly, considering the results of the Arneth counts: Here again we can find nothing on which to base any inference. Two years ago I made a large number of Arneth estimations on healthy subjects, both European and native, and found that compared with what has come to be regarded as normal in England the count in this part of the tropics tends to shift to the left. When I was getting my results together for publication, two papers appeared in the *Annals of Tropical Medicine*, by Scott Macfie (1915), and by Breinl and Priestley (1915), which covered the same ground, and in them the results given were so similar that I saw no object in making my own findings more widely known.

The question of the Arneth count in the cases of the disease



under discussion may be summed up briefly thus: Though the Arneth index is generally higher than that recorded in Europeans at home (about 40), it shows very little difference from what has been found in the blood of healthy Europeans in the tropics (51), and no difference at all as compared with apparently healthy natives (55.9).

The highest index in all of the series given in the table was 69.4, a case of the nervous variety of the disease in an advanced and chronic stage, and the lowest (if we except the uncertain case, No. 28) was in the early stages of a severe and fatal case of the same (No. 19), in which the index was 38.3. The average for the whole series works out at an index of 51.2, or if we exclude the two uncertain cases (27 and 28), at 52.4, or approximately that found in healthy natives.

No inference, therefore, is permissible, unless it be that the condition is probably not a blood infection.

A relative lymphocytosis is well known in the tropics; not only in association with intestinal conditions, such as some of these patients exhibited, but so frequent as to be regarded as almost the normal state.

In the counts given in the table, the lymphocytosis is in excess of what can be looked upon as a normal condition, or even as one frequently encountered. The condition presented by these cases, however, does not correspond with any of those generally noted as associated with an absolute or a relative lymphocytosis, with the exceptions of syphilitic affections and intestinal diseases. The former of these is excluded by the uniformly negative Wassermann reaction. How far the latter fulfils the possibilities will be discussed in the sequel.

## V. SUMMARY OF NERVOUS SYMPTOMS

Table II gives a general summary of the chief symptoms exhibited by the various patients whose histories and physical conditions have already been detailed. A perusal of this table will obviate a long description of the various features presented.

In all cases except one the intellect is stated as good, and it remained so till the end. In the one exception, one might with

fairness state that the fault lay less in the general intellectual condition of the patient than in her memory for details. She replied promptly enough to questions and evidently understood them clearly, but owing to a defective memory her replies were at times contradictory when the questions related to previous events, in particular the onset of her illness. In dealing with the symptoms as set down in the table, it will be better to exclude the last two cases. These were only seen on one occasion, they had been ill for a long period, and it is far from certain whether at all they afford examples of the condition under discussion. They were sent because some of the symptoms presented resembled those found in the Spanish Town outbreak, and the medical practitioner who kindly sent them to me stated that he did so on account of this resemblance; since, however, only prolonged observation could decide the question and the patients had to leave Kingston for the country the same day, no assertion as to the identity of their condition with that under review can be made.

With regard to the remaining nineteen patients the onset occurred in every case comparatively suddenly. The first symptoms were the same in almost every instance—sore eyes and mouth. All suffered with one or other, or both. One stated that her mouth was affected as the first symptom, and that there had been no eye trouble at all, another was a little doubtful on the point, while two stated that the itching and soreness of the eyes had been succeeded in course of time by the nervous symptoms without any intervening mouth involvement.

It will be also seen that the 'intestinal' or diarrhoeal cases never showed any nervous system affection at all, and that none of the 'nervous' cases had any early diarrhoea; all were constipated. This fact has already been noted in an earlier section, and need not be laboured further now.

Passing on to a brief consideration of the nerve affections: All complained of a numbness of the feet and legs. In more than half, this sensation extended above the knees, and in all but one of these in whom this extension took place the upper extremities became involved later, while in four cases the tongue was affected also. In no patient did the latter occur without involvement previously of the hands.

In five instances the girdle sensation was complained of; but in none of these was any zone of hyperaesthesia detected at or above the level of girdle sensation.

In no case was any real 'pain' given as a symptom. Three of the patients mentioned pain; one stated that it was in the knees, but only one movement, and it appeared to be slight; there was no heat or swelling and no pain elicited on passive movement, manipulation of the joints being allowed without resistance. Another stated that she had pains in her arms at night, but, on further questioning, as already stated (case of C. H.), she explained that she did not feel any real pain, but that the arms felt uncomfortable and that she could not place them in a position of ease during the night. A third (T. J.) stated that with the tingling and numbness of the hands he felt 'pains' in the arms, but here, too, movement and manipulation were permitted freely, so that it cannot have been at all severe.

Three only stated that they had any 'crawling' sensations, and tingling was not very common; the noteworthy point about all the cases was that in spite of the extensive area over which they felt the numbness, no change in ordinary tactile sensation could be made out objectively, except in one patient (E. G.), where there appeared to be a slight recognizable deficiency. As stated in the preliminary remarks, all the patients were able to feel the slightest touch when their eyes were bandaged, and furthermore could accurately locate the part touched. In severe cases there appeared to be some affection of the kinaesthetic sense, and weight discrimination was markedly deficient in two. In many, I am sorry to say, this test was not made.

Although no interference with tactile sense could be detected objectively, nevertheless some of the patients affirmed that over the numb areas, although they could feel light touches, the sensation conveyed was 'duller than' or 'not the same' as over the normal parts.

The only sensory change which could be definitely made out objectively was that of discrimination between heat and cold. Even where the differences were great, e.g. cold water in one tube and water recently boiled in the other, confusion often resulted, and, strange to say, the reply was more often to misname the hot tube

and say it felt cold than *vice versa*, and again in many instances where the discrimination was made the sensation was distinctly delayed. The hot tube could be applied for three or four seconds before the patient recognized it as hot, and even then was at times dubious.

In three cases in which the hands and forearms were affected, astereognosis was present, and in one (E. G.) was very marked, as has been noted in the detailed report.

There was no localised wasting of muscles. As the disease progressed to a fatal issue a condition of general emaciation came on, but no true paralysis of any group of muscles could be detected. The movements generally towards the end were weak, but this was merely the result of the exhaustion and not due to paralytic conditions.

The gait was variable, at times inclined to a spastic condition, the feet, as it were, sticking to the ground and shuffling; in many it was ataxic, the feet being thrown about wildly; in none was it really tabetic; in some, again, it was a 'delicate' half-shuffling, half-stumbling gait, while in many it could not be tested owing to the patient being unable even to stand, much less walk. Romberg's sign was doubtful in two cases, negative in all the rest in whom the test was possible.

With regard to incoordination: All those in whom the numbness had extended to the knees showed incoordination of the lower limbs, but in the majority this was much less marked when the patient was lying in bed than when he was up. Those patients whose hands or arms were affected showed a corresponding incoordination of the hands.

Pupillary reactions were normal in all cases except in one who had a somewhat sluggish reaction to convergence; in no instance was the Argyll-Robertson phenomenon present. The field of vision by ordinary rough tests was normal, and there was no instance of strabismus, ocular paresis, or diplopia. In those who were passing to the chronic stage with recovery of general health, a frequent complaint was of 'dark vision.' The significance of this term has been explained in the section giving the details of the various cases. In some of these chronic cases, in patients recovering general health with residual symptoms, as already mentioned, some degree of

deafness was found. This showed itself as a defective nerve conduction.

Taste was normal in all; the testing was performed in the usual way with sugar, salt, quinine, and citric acid. Even in those who complained of the numbness of the tongue no defect in taste could be detected. The reflexes depended apparently to a great extent upon the area affected by the numb sensation. In no case was numbness of the face complained of, though one patient (A. D.) stated that her 'face felt tight, but not numb.' The jaw-jerk was normal in all. The elbow-jerk was doubtful in two patients, and absent in E. G. The wrist-jerk was absent in all those in whom the numbness extended to the forearms. The knee-jerks were lost early in the affection, at all events by the time the patients came under observation. In most cases this was not until the numbness had spread to the knees and made walking very difficult or impossible. The possibility of there being an initial exaggeration must be considered in the light of the patient M. H. In her the onset was slow and irregular, and the knee-jerks at an early stage were exaggerated, but later, as the disease progressed, they disappeared, and the same remarks apply to the ankle-jerk.

Babinski's test is quite unreliable in the native. The skin of the sole is so thick that in 90 per cent. or more no response at all is obtained. The superficial reflexes were in nearly all cases normal, in three they were noted as variable, by which is implied that they were indistinct and obtained irregularly.

In no case was there any sphincter affection. Even in the bed-ridden patients there was never any need for a catheter, and, as stated in the reports on, for example, J. P. and G. P., when the profuse diarrhoea came on at the termination of their illness, there was not the involuntary evacuation of sphincter involvement, but the stools were merely loose and frequent; the patient was always able to inform the attendant of his wants.

## VI. HISTOLOGICAL CHANGES

The changes in the nervous system are very marked and widespread, and, as will be inferred from the description of the symptoms present, there is no picking out of any one system or tract corresponding, for example, with anterior poliomyelitis.

Since the nervous system changes are the most marked and most important, they call for more detailed description than the other organs of the body. The conditions found in the latter will be dealt with first and more briefly.

Parts of various muscles were taken, viz., heart, supinator longus, tibialis anticus, tongue. The skeletal muscles showed the changes about to be described.

*Tibialis anticus*: The transverse striation of the fibres is well marked and the nuclei stain well; here and there, but by no means frequent, one sees a fibre which has poorly-marked striation and in which the tissue appears granular; in such the nuclei stain less well. This condition is shown by the ordinary staining methods—haematoxylin and eosin, haematoxylin and Hansen's modification of van Gieson, etc.

The tissues which have been subjected to the Marchi method or other osmic acid process show, in a fair proportion of the fibres, small black particles which under higher magnification were seen to be globular—fat. These fibres show the transverse striation, but not as plainly as in normal muscle; other fibres appear vacuolated and may contain comparatively large fat-droplets. Fibres showing well-marked striation contain no granules. Affected fibres are apparently picked out arbitrarily, healthy and granular fatty fibres lying side by side.

*Supinator longus*: Similar to above, but in less degree. No fibres seen showing large fat globules; comparatively few show even the small granules, and the number of fibres normal is much greater in proportion. Even those showing most granules have not completely lost their striation. By haematoxylin and Hansen nothing abnormal seen, except that a few of the fibres show some excess of nuclei.

*Tongue*: No atrophy of muscle, epithelium normal, muscle nuclei stain well, striation well marked. No abnormality seen.

*Heart muscle*: The cross-striation is variable in distinctness, in some parts quite plain, in others it is partly obscured. Here and there are seen small patchy accumulations of round cells in the sub-epicardial layer. The longitudinal striation shows plainly.

In the corresponding tissue from another patient the changes are

similar, but in addition there is a slight interstitial myocarditis, with dilatation and congestion of the cardiac capillaries. The muscle-nuclei as a whole stain well. By the Marchi-Alghieri method, minute granules and droplets stained black by the osmic acid are fairly generally distributed throughout the muscle tissue. Occasionally one sees a fibre showing no proper striation, and here the granules are massed together, in some situations aggregating to form minute droplets. Some of the granules are of a browner colour, and may be pigment, not fat; in favour of this is the fact that many of the fibres showing numerous granules have well-marked striation and no signs of degeneration, but on the other hand sections stained with haematoxylin and van Gieson (Hansen's modification) which have therefore passed through alcohol and xylol, show no granules, thus pointing rather to their fatty nature.

*Lung*: Some degree of emphysema. Vessels are congested and the alveoli in isolated spots contain red blood cells. In other places there are localised areas of broncho-pneumonia, the alveoli containing red cells, leucocytes and shed epithelium, adjacent to distended emphysematous alveoli, and the bronchioles have also lost some of the lining epithelium.

*Spleen*: Haematoxylin and Hansen. In the one case the capsule is thickened; Malpighian corpuscles well marked; vessel walls thicker than normal, and fibrous trabeculae prominent. There are pigmentary deposits (brownish black) scattered irregularly throughout the pulp, not more numerous in the neighbourhood of the vessels. In the tissue from another patient there is no excess of fibrous tissue, nor thickening of the vessel walls; very little pigment seen.

In Marchi sections there is considerably more black staining than in the haematoxylin sections, pointing to the fact that in addition to the pigment noted above there is also some fatty metamorphosis or deposit, which latter had been removed in the preparation of the tissue for the haematoxylin but retained by that for the osmic method. Under the higher powers the brownish-black granular pigment can be distinguished from the globular, black fatty deposits.

*Liver*: Haematoxylin and Hansen. G. P. showed accumulation of small round cells and early fibrosis in places, especially round the portal system. Also subcapsular accumulations of similar cells, and

here and there beneath the capsule are spaces filled with blood corpuscles; the outer edge being limited by these small-celled accumulations. In one part of the liver the development of fibrous tissue is more marked and in its neighbourhood are spaces filled with red blood cells, the liver cells showing as mere strands, as it were, resembling an angiomatous condition. Cell-nuclei stain well. The fibrous strands pass in from beneath the capsule and divide the tissue into lacunae containing blood, the liver cells in small masses looking like islets with thin connecting strands in a lake of blood. In the other case there is similar small-celled infiltration but in larger masses, apparently mostly in the region of the portal canals; the liver cells in such situations appear 'rarefied' and partially displaced. These parts resemble alveolar tissue with small cells and liver cells in the meshes. The line of demarcation between this condition and normal liver cells is moderately abrupt.

*Kidney:* Haematoxylin and Hansen. The nuclei in glomeruli stain well, but in some instances the whole glomerulus is shrunken from Bowman's capsule. There is slight increase of the interstitial tissue. The nuclei of the secreting epithelial cells stain well on the whole, but in places the protoplasm is granular and stains poorly, especially that of the convoluted tubules and the ascending tubules of the loops of Henle. In one situation there is a marked localised development of fibrous and unstriped muscle tissue, fairly abruptly demarcated from the surrounding renal tissue; there is no small-celled infiltration, no caseation, nuclei stain well.

Marchi. In tubules with degenerated epithelium minute black granules and droplets are seen, not marked in the convoluted tubules. The tubules so affected, however, are not relatively numerous, though by the 1/12 in. very small dots may be seen in many in which they are not recognized by the lower powers. The cells of the glomeruli occasionally show the same condition, but the affection of these is very slight. Under the high magnification it is noticed that the majority of the tubules show very small black dots and granules. They may also be seen in the vessels, but not commonly, nor are the droplets at all large there.

In Marchi sections the glomeruli are seen not to be so shrunken from the membrane, and the condition present in the haematoxylin section is, therefore, probably an artefact in the preparation.



In the second patient, except for a slight increase of intertubular connective tissue, the appearances are nearer normal. The renal epithelium shows well-marked nuclei, though the cell-limits themselves are not well defined. The droplets and granules also are much less numerous than in the previous case.

Though many of the 'particles' are globular in shape and black, others appear more of a dark brown, amorphous, pigmentary deposit.

No organisms, bacterial or protozoal, seen.

*Adrenals:* Very little departure from the normal seen by the haematoxylin method, no pigment visible, and the nuclei stain well. In some parts the cells appear a little more granular, and some give a faint suggestion of vacuolization. By the osmic acid staining the majority of the cells show black granules, which in many instances have coalesced to form spherical droplets. The interstitial tissue shows a similar deposit of black granules, but here they are smaller and have not coalesced. The zona fasciculata seems to show the condition in most marked degree; the reticulata least.

*Pancreas:* Nothing abnormal by the low power; nuclei stain well; islets normal, no engorgement of vessels; with higher power the glandular epithelium is seen not to stain well and shows minute vacuoles. Many of the glandular epithelial cells by the osmic acid method show similar granules and droplets to those already described. The acini affected are not confined to any particular spot, but irregularly distributed, one group perhaps showing the change extensively while adjacent groups are very little affected, or almost normal. In some places it would appear that those cells nearest the vessels show the greatest change, but this is by no means general.

In this organ much of the deposit is rod-shaped and granular rather than in droplets.

*Gastric mucous membrane:* In one patient, G. P., there is a small area of denudation of the epithelium, but nothing else abnormal is noticed. In the other, J. P., no abnormality is detected.

*Small intestine:* In G. P. the mucous membrane appears to be generally normal; the nuclei stain well and the cells are distinct. In two situations in the section there is an accumulation of round cells beneath the muscularis mucosae, but no distension or engorgement of the vessels, no pus formation, no giant cells, no caseation,

no pigmentation. In another spot this heaping up of cells had thrust through the submucous coat to the mucous layer, which is being denuded.

In J. P. there is considerable congestion of vessels beneath the mucous membrane and dilatation to form a picture of blood sinuses or extravasations into inflammatory connective tissue. In this patient there are several places in which the mucous membrane epithelium has been shed and small erosions found.

*Large intestine:* Shows well the localised accumulation of small cells with occasional shedding of the overlying mucous membrane. The submucous blood spaces are lined by endothelium, and are more distinct than in the small intestine.

*Mesenteric glands:* In G. P. the capsule in some of these is a little thickened, the gland tissue itself is hyperaemic and the vessels distended and engorged. In the case of J. P. there is similar congestion, but no thickening of the capsule is seen.

It may be stated here that sections of all these tissues and also of all the various parts of the nervous system were stained for organisms by various methods—Giemsa, Löffler, Eosin-Gram-Weigert, Gram, Carbol-fuchsin—but no organisms were detected.

We pass on now to the description of the various parts of the nervous system which were submitted to microscopical examination.

*Median nerve:* Marchi. G. P. Brownish-black and black deposits granular and in droplets; in some of the fibres mostly granular and in masses. A large proportion of the fibres are unaffected; here and there a fibre shows the black of the Marchi staining, but the fibres so affected are relatively not numerous. It is noticeable that there may be several in one bundle, while those in the vicinity show none. Even in those with the most staining, the deposit is more of the diffuse brownish stain and not as droplets of broken-up myelin. In transverse section it is quite rare to see a nerve fibre with a distinct black ring of degenerated myelin.

J. P. In this patient the nerve fibres themselves are even less affected. In transverse section it is noticed that the nerve fibres themselves are many of them untouched. Minute droplets are seen in the fibrous tissue and in the walls of the vessels.

*Sciatic nerve:* Bundles cut longitudinally show considerable

general brown staining; also black, granular and patchy deposit, at times in droplets. These, however, seem in many cases to be more of the nature of a deposition of the stain *on* rather than *in* the nerve fibres, and in bundles cut transversely it is comparatively rare to see a fibre showing the stain, while granules are visible in the perineurium and in the vessel sheaths. No congestion of vessels, nor increase in fibrous tissue is noticed.

Some of the fibres cut longitudinally do show fragmentation of myelin and droplet formation, but such are not very numerous.

Other methods of staining do not reveal any abnormality.

*Ulnar nerve:* G. P. The change here is much more extensive than in other nerves. The majority of the fibres in longitudinal section show fat droplets, some exhibiting large droplets in series along the whole length of the fibre shown in the section; others have smaller droplets scattered at intervals along the course of the fibres.

J. P. In the corresponding section in this case there is very little involvement, hardly any of the fibres show the large droplets and fragmentation, and only a comparatively small proportion reveal any degeneration at all; the majority of the fibres are unaffected.

*Posterior Root Ganglion: Cervical:* G. P. A majority of the nerve fibres in this section show a black deposit in granules and droplets, and fully half are extensively affected. Many of those cut longitudinally appear as a series of droplets along the course of the fibre, and of those cut transversely the axis cylinders are surrounded by a black ring of myelin.

The large ganglion cells are much affected; many of them reveal a protoplasm almost entirely converted into black dots, in the midst of which, by careful focussing, the nucleus can be seen; others show a more peripheral distribution of granules, the nucleus being quite distinct; while yet again others contain merely a few fine granules in some part of the cytoplasm, usually distant from the nucleus, which is eccentrically situated.

J. P. In this patient the corresponding sections, though showing analogous conditions, nevertheless exhibit them in much less degree. The proportion of fibres affected is comparatively small, and it is only rarely that one is seen containing large droplets, and of those cut transversely only 1 or 2 per cent. show the distinct black ring

round the axis cylinder. Also the ganglion cells show none of the grosser changes mentioned above; the utmost seen is a cell with an eccentric nucleus and a small patch of fine granules somewhere in the protoplasm. Many show no abnormality at all.

*Dorsal:* G. P. More deeply involved than the cervical root ganglion; very few fibres have escaped.

J. P. In this the condition is practically the same as in the cervical region as regards the fibres; the numbers involved are certainly not more than in the cervical (thus differing from G. P.) and the ganglion cells show but slight changes.

*Spinal Cord. Cauda equina:* The fibres of the equina show fatty changes to varying extent in different parts. In those showing the greatest involvement about 25 per cent. of the fibres are affected, but in most parts the proportion is much below this, only a small proportion of fibres being degenerated.

*Lumbo-sacral cord:* The posterior columns show considerable degenerative staining fairly generally distributed, but possibly a little more marked in the external parts, and only slight in the ventral field of the posterior root zone. The radicular zone is considerably affected also, but more towards the periphery. Lissauer's marginal zone shows much blackening also.

The antero-lateral ascending tract shows some involvement, and in the lateral ground bundle there is a slight, generally distributed black stippling and degeneration of the long and short association fibres. The site of the tractus rubro-spinalis shows practically no degeneration, and the anterior and lateral vestibulo-spinal tracts also are but slightly affected.

Dotting of degenerated fibres is also seen in the regions of the spino-thalamic and spino-tectalis tracts, and possibly in the corresponding descending fibres (thalamic and tecto-spinalis); the anterior tecto-spinal tract shows considerable involvement.

Little change is visible in the lateral pyramidal tracts or in the direct (anterior).

No affection, or very slight, is seen of the fibres in the anterior commissure, though numerous scattered droplets are noticeable in the fibres of the anterior ground bundle. The various groups of the cells of the anterior cornua are all involved, but the dorso-lateral, intermediate and ventral all to a greater degree than the medial.

*Lower Lumbar Cord:* The posterior columns consist largely of fibrous tissue with masses of fat. Some fibres have escaped, but unaltered fibres are by no means numerous. There is a little perivascular infiltration, and phagocytes are visible bearing fat.

There are fatty fibres dotted here and there, but less marked than in sections higher up. It cannot be said that any particular tracts are markedly singled out. The various tracts affected are the same as those described in the section of the lumbo-sacral cord, with one or two minor differences. Thus, the marginal root zone shows more staining, and possibly also the vestibulo-tecto-spinalis and thalamic tract areas. The cells of the anterior horn are fairly involved, but, as before, the medial group less than the others. Most of the cells contain collections of coarse granules and fat, though showing no obvious changes in the nuclei. The anterior commissural fibres show some staining.

*Middle of Lumbar Enlargement:* There is no appreciable difference noted between the affections of the tracts in this section and the last, except that the degree of involvement of the posterior columns appears more marked.

*Upper Lumbar Cord:* The posterior columns here show considerable fatty degeneration and fibrosis. The perivascular infiltration, which is quite noticeable higher up the cord, here is but slight, but leucocytes, containing fat may be seen more or less throughout this part (posterior column). The remainder of the section shows scattered degenerated fibres. A similar condition is now present in the dorsal cerebellar tract, but less than in the antero-lateral ascending. The cells of Clarke's column mostly exhibit considerable granular degeneration and chromatolysis.

*Lower Dorsal Cord:* The relative fibrosis and the fatty degeneration of the posterior columns continue to increase as the cord is ascended; the perivascular infiltration again is less marked than in the upper and mid-dorsal regions. The beginnings of the direct cerebellar tract show fatty changes, and the cells of Clarke's column are very heavily charged with fat. There is some, but not very marked involvement of the ventral part of the posterior root zone, while those fibres of the posterior columns entering the root zone medial to the posterior horn (? Schultze's bundle) are more affected. The postero-medial root zone and the marginal zone are markedly

involved. The crossed pyramidal tract shows very little change, as does also the direct. The fibres contiguous to the sulcus, the fasciculus sulco-marginalis (tecto-spinalis anterior), show definite fatty degeneration.

The areas of the anterior ground bundles show scattered droplets. The cells of the anterior horns are definitely stippled, and those of the dorso-lateral and intermediate groups rather less than those of the ventral and medial.

*Mid-dorsal Cord*: The posterior columns are still more extensively affected; there is much apparent fibrosis, partly caused no doubt by the disappearance of some of the fat, but the tissue entangles, as it were, large globules of fat. In some sections numbers of endothelial cells containing fat are seen, and there is perivascular infiltration with fat-bearing cells. The posterior root bundles are very fatty, but not so deeply affected as Goll's column itself. The direct cerebellar tract is severely involved, fully half the fibres appearing degenerated. The crossed pyramidal tract shows only occasional fibres with fatty changes. The antero-lateral ascending has the majority of its fibres attacked. The cells of the anterior horn show, many of them, fatty degeneration, and this change is present to quite the same extent, in fact more, in the cells of Clarke's column. The marginal zone shows a mass of black fibres. In the lateral ground bundles only scattered fibres are seen affected, but the anterior marginal bundle (? vestibulo-spinalis) is badly degenerated.

*Upper Dorsal Cord*: The fatty degeneration is so marked that it is difficult to make out whether one part is much more affected than another, with the exception of the following where the involvement is comparatively slight, namely, the crossed pyramidal tract, the lateral ground bundle and the commissural bundle. Of the remaining parts the most intense changes are seen in the posterior columns, the marginal and posterior root zones, the dorsal and ventral cerebellar tracts, and the anterior marginal bundle. Where the nerves appear also in the section it is noticeable that the majority of the posterior fibres entering the cord are markedly degenerated, as compared with the considerably smaller proportion of the anterior passing out.

*Cervical Cord*: The whole of the posterior columns show extensive degeneration, less marked in the ventral field of the posterior root

zone. The marginal root zone is greatly affected also. Mingled with the fat in the posterior columns is seen an excess of fibrous tissue, though some of this may be apparent only from removal of a portion of the fat. There is considerable perivascular infiltration, the perivascular lymph spaces being in parts almost choked with fat-containing cells.

The direct cerebellar tract, though extensively involved, shows a little less change than that in the antero-lateral. The lateral ground bundle is less altered than other parts, and here the area most affected appears to be the spino-thalamic fibres, and in the anterior ground bundle the corresponding fasciculus sulco-marginalis. The anterior vestibulo-spinal tract area is also deeply stained. The pyramidal tracts have not by any means escaped, but compared with the sensory areas there are only a few scattered fibres degenerated.

Cornual cells show much stippling with fat granules, more marked in the dorso-lateral, intermediate and ventral groups, less in the medial.

*Medulla:* There is marked degenerative staining of the funiculus gracilis, less, but still very distinct, in the funiculus cuneatus; the substantia gelatinosa shows very little change. The direct cerebellar tract is markedly affected; the crossed pyramidal tract but slightly. The cells in the anterior cornua of grey matter are only involved here and there, and then only minute dots are seen.

In the fissure of the upper part of the cord and round the central canal, sections of tissue treated by the Levaditi silver impregnation method, black, bacillary, rod-shaped bodies are seen. These, however, are probably only fat, as none of the ordinary methods used in searching for bacilli (Giemsa, Löffler, Eosin-Gram-Weigert, Gram, Carbol-fuchsin, etc.) showed any of these bodies, the preliminary treatment with alcohol and xylol having, as I interpret it, led to their solution and removal.

*Pons Varolii:* Except in the pale areas there is a general distribution of the fatty metamorphosis, but in small masses in the neuroglia, possibly due to the removal of the fat there, leaving the connective tissue more prominent. The cells themselves are fairly generally affected also, but in a minor degree, as a faint dusting of granules. The cells of the vestibular nerve root show considerable degeneration, mainly peripheral to the nucleus, both the descending root and the

principal nucleus. There is a patchy distribution of the staining in the general ground work, especially in the *formatio reticularis*. The *substantia gelatinosa* shows practically none; while the fillet is considerably involved. There is slight 'dusting' of the cells of the VIIth and also of the superior olive, none of the central tegmental tract.

In the case of J. P. the deposit is very much less than stated above in the case of G. P. The groundwork shows some, but hardly any cells are affected at all.

Throughout the cord sections the description given is made mainly from examination of the tissues taken from G. P.; in the case of J. P. the distribution is seen to be similar, but the degree of involvement throughout is much less.

*Cerebellum*: In G. P. the cortical layer shows very occasionally cells with a few minute black droplets; the Purkinje cells are mostly intact, a few contain very minute granules and exhibit chromatolysis. In the interior—the nuclear layer—of each branch of the 'arbor' there is marked degeneration. Some of the vessels also contain fat-droplets. In J. P. a similar condition is seen, but in much less degree. Only one or two cells in the cortex are involved; no Purkinje cells appear to be affected; a few granules and larger fatty masses are seen in the inner (nuclear) layer, where the change is most marked in G. P. The vessels here, too, occasionally contain a few droplets.

*Superior Peduncle*: G. P. Patchy staining similar to that already described, affecting the groundwork, but the cells are nearly all involved, showing numerous granules and droplets; the nucleus, though indistinct in some cells, is still recognisable in almost every instance.

In J. P. the degree of involvement is quite slight, and is mainly confined to the white substance; a small proportion of the cells also is affected, but very small as compared with G. P.

*Cortex Cerebri*: Frontal. A considerable number of the large cells, varying in the different sections, exhibit the granular deposit, generally of the periphery, occasionally throughout the cytoplasm. In the latter case the granules are coarser and the droplets larger at the periphery. The fibres in the cortical grey matter are not affected, but in the white subcortical region there is extensive granular



patchy staining with the Marchi fluid. In the other case a similar condition of things is present, but less extensively distributed; there are fewer cells involved and less affection of the subcortical layers.

*Motor Cortex*: In this part the cells are much less affected both in degree and in proportionate number, but the deeper fibrous layers are more extensively involved than in the frontal region.

In both parts, whether the cells show merely a fine stippling or masses of minute droplets of fat, the nuclei of the cells appear to be unaffected, and further, although the white matter contains the droplets, as stated, all over, it is difficult to say whether it has any definite relation to the nerve fibres.

*Optic Thalamus*: A generally distributed black staining of the fibres is visible, but by far the most marked change is seen in the cells of the granular matter, which nearly all contain many large droplets, sufficient in many instances to obscure the nuclei.

*Lenticular Nucleus*: Appears to be practically uninvolved. Here and there one may come across a cell showing a few granules and a little chromatolysis, but such are far from common. The fibres in the neighbourhood show a patchy and granular deposit.

*Corpora Quadrigemina*: Many of the large nerve cells contain fat in somewhat coarse granules, which may more or less fill the cytoplasm. Throughout the section may also be seen a number of fatty nerve-fibres. Even those cells which contain many granules seem for the most part to retain their nuclei intact.

*Hypophysis*: Sections of this organ show extensive granular staining with the osmic acid. Every cell apparently has granules, either few or many. The fibrous elements, however, and also the vessels and capillaries exhibit none.

*Auditory Nerve*: Several fibres contain very small granules, in fact, the majority, while the grey matter shows fatty changes in the large nerve-cells, but not marked.

*Optic Nerve*: Widespread degeneration distributed along practically all the fibres; very few have escaped.

In the sections of the optic chiasma the large nerve-cells contain in some cases masses of fine fat granules.

*Olfactory Lobe*: Sections of this reveal considerable affection of the nerve fibres; the large cells, however, are very slightly involved;

here and there may be seen a cell with black granules and droplets, especially at the periphery remote from the nucleus.

Microphotographs are appended to illustrate some of the points mentioned above.

## VII. DISCUSSION

Having given accounts of the histories, symptoms, physical signs, and morbid anatomy of this condition, we are justified now in discussing the important question: 'Are we dealing with a new disease?'

The question will be dealt with under the following heads:—

1. Is it Pellagra?
2. Is it Beri-beri?
3. What relation, if any, does it bear to the so-called 'Peripheral Neuritis' in Jamaica?
4. Is it a new 'deficiency' disease?
5. Is it microbial in origin?
6. Is it an intoxication?

These questions are somewhat interwoven, but in order that the matter may be presented as lucidly as is in my power, and afford a basis for future discussion and investigation, they will be kept separate as far as possible.

1. In the ensuing discussion as to the probability, or even possibility, of the condition being pellagrous, I have made free use for comparison of the report of the Second Triennial Meeting of the National Association for the Study of Pellagra (1913), and I beg to preface the points about to be brought forward by acknowledging my indebtedness to that report.

Firstly, as regards the onset. In Pellagra, the report states (p. 41): 'on account of the vague nature of the early symptoms of the disease it was impossible to determine the exact date of the onset of the first attack in all of them. The year of onset, however, was determined in 317 of the 323 cases, but the month of onset was determined with a fair degree of accuracy only in 181.'

Now, in contradistinction to this, in the Spanish Town cases, not only was the year or month certain, but the actual day and hour of onset known. Also, in none of them could any history be obtained of a previous attack in the same patient; there is only one which

either terminates fatally, or becomes chronic, or clears up entirely, or, lastly, partially clears, leaving residual symptoms.

In pellagrous districts, as recorded in the report, the largest number of cases in which the month could be determined occurred in May and June, with a gradual rise to the maximum, then a gradual decline during the succeeding months. Whereas the majority of the Spanish Town cases occurred in March, April and early May, and then the presentation of fresh cases suddenly ceased (a likely explanation of this will be given later).

As predisposing causes of pellagra, it is mentioned that the patients lived in squalid surroundings, were poor, overworked and underfed (p. 73). Although some of my cases at Spanish Town lived in squalid surroundings, they were certainly not overworked nor underfed. Almost without exception they said that they had had plenty of food, usually yam, bread-fruit, and such like, but the cane crop being then cut and carried, they were living practically exclusively on cane. As regards food, the pellagra report states: 'Despite the rural location of the homes of the pellagrins of the agricultural class, they, too, were found to depend to a considerable extent for their food upon the country grocery store. It was the exception to find a pellagrin who could state that even the major part of the food used in the family had been home-grown.'

'Much of the food had undergone some process for its preservation, such as desiccation, canning, etc.'

In my cases the reverse conditions prevailed. In ordinary times they relied (with the exception of salt-fish obtained at a store) upon home-grown articles, yam, bread-fruit, cocoa, peas, beans, and so forth, and, as already stated, during the crop-time they lived on sugar-cane. Grimmon gives the following in his summary (p. 49):—

*Race:* More cases developed among the whites than among the negroes.

In the Spanish Town cases no white man was attacked at all; only West Indian labourers on the cane fields.

*Sex:* More cases occurred among the females of both races than among the males.

The distribution was practically equal at Spanish Town.

*Age:* More cases developed at ages between 20 and 40 than at other ages.

This also obtains in my cases; in fact, all of whom I have detailed

records were adults except one, a girl of 14 years, and she was earning her living by labouring on the estate.

*Date of Onset:* More cases had their onset during the months of May and June than in other months.

This has already been referred to above.

*Relationship of Cases:* More cases developed in the vicinity of other cases than otherwise.

This point is not of much use as positive evidence, it is equally in favour of a common source of origin.

*Heredity:* None of the facts seem to indicate that pellagra is hereditary.

On p. 113, Professor Victor Babes states: 'In spite of the rich literature on pellagra, scarcely so important a malady exists about which we are so badly oriented. One thing only seems to be established about its etiology: that it belongs to the disease of poverty or insufficient alimentation, and notably that it is in intimate relation with nutrition by maize of bad quality.'

With regard to the Spanish Town cases, they occurred, it is true, amongst the poor, in so far as labourers are not well-to-do, but they were not destitute; although the cost of food was high at the time, this fact did not affect them to any appreciable extent as they lived on the cane which they took while at work, and if they had anything else it was merely the usual ground provisions; they do not eat maize to any extent, particularly in the cane season; at other times they use it as cornmeal. Practically all said that they were getting plenty of food.

Of fifty cases of pellagra in which the history of the onset was obtainable, only one of those recorded in the pellagra report (p. 121) bears any resemblance to the Spanish Town cases, and that is not a close one. The account states that the disease began 'just before Easter, weakness, disinclination for work, tingling sensation in the hands and feet. At the end of a week, erythema.'

In my cases the onset was in all instances sudden, there was no previous weakness or disinclination for work, that is to say, no abnormal disinclination (of course, it must be remembered that all West Indian natives, as soon as they are old enough to work at all, exhibit a disinclination for work). Eye or mouth symptoms, or both, without exception, preceded any nerve symptom; these latter were

not tingling, but numbness, and began in the feet several days, perhaps two to three weeks, before any similar symptoms appeared in the hands; and, lastly, in none of them did any erythema follow, even when watched for months.

Again, one of thirty cases of pellagra described in detail by Dr. Deeks (p. 182) bears a superficial resemblance to the Spanish Town cases:—‘L. B., Martiniquan, coloured, male, aged 40, admitted July 13th, 1910, complained of having been sick for eight days and unable to work because of pain in the joints and extremities. On admission the temperature was  $110\cdot4^{\circ}$  [probably a mistake for  $101\cdot4^{\circ}$ ], pulse 128, and respirations 54. Patellar reflexes absent; Romberg’s sign present; gait ataxic; unable to coordinate. He had the characteristic oral mucous membrane but no dermatitis. From the mid-day of his admission he vomited almost constantly, was nervous, slept badly, and developed an uncontrollable diarrhoea; temperature increased, and he died with a temperature of  $106^{\circ}$  on the fourteenth day after his admission.

Leucocytes on admission: polymorphonuclears 81 per cent., large mononuclears 4 per cent., small mononuclears 15 per cent.’

The points of resemblance are: (1) The patient was ill for eight days before any nervous symptoms presented themselves. (2) Absence of patellar reflexes. (3) Ataxic gait and incoordination. (4) No dermatitis, but sore mouth. (5) Diarrhoea towards the termination.

The points of difference: (1) Pains in the joints and extremities; the former was slight in some cases of the Spanish Town series, but not definite pain even then, and movement was always quite free and painless. (2) Rise of temperature, rapid pulse and respiration; all of these are absent in my cases. (3) Romberg’s sign is absent, when the patient can stand well enough for this to be tested. (4) Vomiting was never a symptom in any case.

In short, except for a few symptoms, there is nothing else common to both, and the general picture is quite different.

Of the blood changes in pellagra, Hillman writes: ‘Examination of the stained preparation of the blood revealed very little change in structure or staining reactions of the red cells; some irregularity in size was noted in a few cases, microcytes appearing to be the most common form. No nucleated cells were seen.

'The differential leucocyte counts showed the most important and constant alterations (500 cells were counted as routine). . . . The cells increased were chiefly the small lymphocytes. Including both large and small types of lymphocytes, the percentages in the more pronounced cases ran as follows:—43·00 per cent., 36·00 per cent., 50·35 per cent., 47·20 per cent., 52·00 per cent., 41·80 per cent., 40·00 per cent.

'The majority of the pellagrins show a relative increase in the lymphocytes at the expense of the polynuclear neutrophils. As to the large mononuclear leucocytes the differential counts show, on the whole, a slight increase in most cases, rising as high as 5·6 per cent. in one instance.

'The polynuclear eosinophiles maintain a normal average in most cases, but in three were in excess, amounting to 8·00 per cent., 7·80 per cent., and 5·40 per cent. Other causes of eosinophilia were not demonstrated in these patients. The average eosinophile count in this series (twelve cases) was 2·86 per cent.'

Summing up, he states 'The increase in lymphocytes is interesting, and what one might expect in a disease associated with a disturbance in gastro-intestinal function and structure . . . . In pellagra we probably have to deal with a disease associated with a rather low grade toxin of some nature, which, in common with many other pathological states, is absorbed by the lymphatic system and through local irritation of certain lymph nodes produces an increased circulatory activity in these situations, in consequence of which large numbers of lymph elements are swept from the lymphatics and enter the general circulation. This is in accordance with Ehrlich's theory of lymphocytosis. The large mononuclear leucocytes are not sufficiently increased to warrant drawing any definite conclusions.'

The blood findings and blood picture of the Spanish Town cases have already been dealt with in some detail, and need not be repeated again here. A comparison between Hillman's findings and mine may most easily be made by a perusal of the Table I of this report, when the resemblances will be seen to be considerable.

The nervous histo-pathology of pellagra has been ably described by Singer and Pollock, and a comparison of their findings with those given above of tissues taken from the cases of the Spanish Town disease will show that there are many points of resemblance.

*Pia mater*: In their cases there was some degree of thickening with an increase in fibroblasts and an infiltration with cells which were derived mainly from the vessels, belonging to both the endothelial and the adventitial types. In some there were a few lymphocytes, and occasionally extravasated erythrocytes. They found as a constant feature the presence of pigment granules. The change was most marked over the convexity of the brain in the central, frontal, and temporal regions, and particularly in and adjacent to the sulci. In the latter situation especially they describe a growth of glial fibres into the pia.

In the larger arteries there was hypertrophy of the muscularis and thickening of the vessel walls, while the smaller vessels showed proliferation of the cells, endothelial, muscular, and adventitial, and some degree of perivascular infiltration made up of lymphocytes and vessel cells.

In their cases the difficulty naturally arose of distinguishing to what extent the changes were due to the pellagrous condition or to the accompanying mental or nervous disease. The vessels showed a moderate proliferation of the cells of the adventitia and media, and, in a few, there was an increase of the intima. The muscle cells were swollen, distorted, and contained granules of pigment. In the sheath they noted fatty and fibrinoid pigment. The perivascular infiltration was not marked.

There were similar changes in the vessels of the spinal cord, and a more or less definite increase of connective tissue along the septa. Dilatation of the small vessels in the grey matter of the cord was marked in some of the cases. This is very distinct in some of the Spanish Town sections. The neuroglia fibres were increased at the outermost layer of the cerebral cortex, and in the spinal cord about the central canal. They state that the satellite and the Trabant cells were increased about the ganglial cells, which showed the true Nissl changes.

The glia cells of the outermost layer of the brain cortex were frequently seen distorted, darkly staining and shrunken, showing intranuclear metachromatic granules. The small cortical glial cells were increased in number, and at times were noticed to form considerable masses about the vessels. In all cases some degree of fatty degeneration of the glial cells was found. The central canal

was occluded in all cases; this is not abnormal, and is seen in some of the sections of the Spanish Town cases. In their cases, however, the occlusion was not due merely to general débris and degenerated epithelial cells, but to a definite proliferation of the glia and ependymal cells, constituting to all intents and purposes a central gliosis.

This was not seen in my cases.

The authors affirm that the axonal reactions in the nerve cells are more definitely related to acute pellagra. The cell is swollen and rounded, the nucleus displaced to the periphery and may even be extruded. The tigroid substance has mostly disappeared from the central portion of the cells, blocks staining well being often left around the periphery and especially in the base of the larger dendrites, a considerable mass being often found around the nucleus. The nucleus is distorted, often oval or reniform, and stains more or less uniformly, with a pale colour.

Axonal changes are less marked, and may be quite absent in long-standing cases or in the interval cases. It is less noticeable in a patient dying three and a half months after an attack, and absent in one dying eighteen months after.

These were not conspicuous, however, in the Spanish Town cases, in those dying after a brief illness.

They further state that in recent cases axonal changes were severe in all, and in many involved practically all the Betz cells and many of the large pyramidal cells of the central convolutions. They found similar changes in the ganglion cells of the hippocampus, the dentate nucleus, the central ganglia, and the nuclei of the cranial nerves.

In the cord these changes in the cells of Clarke's column were often extreme, and in the anterior cornual cells in two-thirds of the cases, in the posterior cornua in one-third, and in one of them more marked than in the anterior. Similar reactions were found in the posterior root ganglia, and in the cells of the semilunar ganglia of the sympathetic and of Auerbach's plexus in the intestine.

Some Purkinje cells showed central chromatolysis, but none the true axonal change.

'The cell showing axonal reaction is, except in very severe degrees, capable of recovery, and the above facts would suggest that



the change is the result of the condition, whatever it is, which underlies the acute pellagrous outbreak. During the intervals the cells again resume, to a greater or less extent, the normal state. 'This type of reaction also seems to result from an injury to the neurone at a distance from the cell, and such an hypothesis is well borne out by the absence of satellitosis about these cells.'

They describe six types of Nissl changes, all of which are most marked in the central and paracentral convolutions, but are also present in various regions of the cortex. These types are :—

1. The cell-body may be shrunken and distorted, staining more or less uniformly pale, with a nucleus rich in chromatin.
2. Similar bodies with pale nucleus of the same or lighter colour than the cytoplasm, and containing bodies stained bluish-green with thionin.
3. Shrunken uniformly dark-staining cell-body and a dark nucleus which may almost fill the cell.
4. Simple chromatolysis, the body being of normal size or a little larger. The Nissl granules may be pale and rarefied, or present merely as dust. The nucleus has a dark nucleolus, but is itself approximately normal in staining and position.
5. As a more extreme degree of the last, where the outline of the cells is indistinct, the nucleus is absent—a mere shadow cell.
6. Vacuolated cells with a nucleus, but showing no Nissl bodies.

Pigmentary changes were present in all their cases and in all the various types of cell-changes, even in those showing normal staining, but marked in the Betz cells, the large pyramidal and other cells showing axonal changes. The pigment stains black with osmic acid, and in some cells within the nucleus there may be basophile and fibrinoid granules.

It must not be forgotten that some degree of pigmentary deposit of a fatty nature is to be considered as a normal condition—a result of failure to remove all metabolic products, whether due to faulty elimination or excessive production, or they may be the result, as Victor Babes has suggested, of degeneration of the chromatin material of the cell.

In pellagra, however, they far exceeded the amount present even in old age, and so far they must be regarded as pathological.

Nerve fibril changes consisted of agglutination, fragmentation, and loss of fibrils, which is exceptional in pellagra. The fibrils are now regarded as of great importance in the performance of the nervous functions of the neuron. Complete loss of fibrils, would, therefore, entail loss of function, and probably a consequent impossibility of recovery of the neuron. In all their cases a marked paucity of processes was noticed in the larger cells. The architecture of the cortex was not much disturbed, in the deeper cell layers of the Rolandic region there was some distortion of arrangement and a paucity of cells. This was noticed in the Spanish Town cases.

Marchi-treated tissues showed in the brain a diffuse, scattered degeneration of the radial cortical fibres, but not of the supraradiary or tangential. In the spinal cord there were 'degenerated fibres in all regions, not in any way systematic, involving perhaps to the greatest extent the posterior columns, and especially the subpial fibres in two cases. The crossed pyramidal tracts were not more affected than other regions, and in some cases were practically free.'

The anterior and posterior roots showed a few degenerated fibres, sometimes more marked in the cervical, sometimes in the lumbar region.

In sections of the cord the loss of stain in Goll's column was most marked in the centre, bordering the middle line. In a few it extended forward to the commissure, and in some back to the posterior surface where it outlines exactly the whole column. Under a high power the degeneration was seen to affect quite scattered fibres, the majority being well stained; and from its situation seemed to involve the endogenous fibres rather than the main ascending tracts. It was most marked in the cervical region, and might in some cases be entirely absent in the lumbar and lower dorsal. In two cases a similar pale staining was found in the crossed pyramidal tracts, in three in Lissauer's tract, in one in the lateral basis bundle, and in two in the posterior ground bundles.

Older authors claimed to find definite systemic degeneration, generally a combined postero-lateral sclerosis. Later work, however, seems to show clearly that systemic degenerations are certainly exceptional and were not present in the cases studied by Singer and Pollock.

Amyloid bodies and pigment granules were found in excess in all cases, and might be numerous both in brain and spinal cord. They were described beneath the ependyma, along the vessels, in the thickened glia of the most superficial layers of the cortex, and the periphery of the spinal cord, and also around the central canal. Though their significance is not clear, they undoubtedly occur, especially in chronic degenerative conditions.

Their origin is not yet determined, so far as I am aware, but they are considered to represent degenerated axis-cylinders or myelin sheaths (Siegert Wolf) or glia cells (Obensteiner) or to be degeneration products occurring within the glia-cell body, which are at first surrounded by a layer of fat, and on the disintegration of the cell they are set free and the fatty circumference is dissolved; again, they may result from the precipitation of certain materials from the tissue juices by the fixing fluids, and thus be in some degree a post-mortem artefact.

If the above description of the pellagral nervous tissue findings be compared with what has been written earlier of the findings in my cases at Spanish Town, it will be seen that there are indeed remarkable points of resemblance, especially in the generalised distribution of the degenerative changes in the spinal cord; but, as stated in my description, though not exactly picking out any definite system in the cord, the changes throughout are much more marked in the sensory conducting tracts than in the motor, and the symptoms present would lead one to expect this.

It must be remembered that free pigment granules of a fatty nature in the tissues and perivascular lymph spaces, and the pigmentary degeneration of nerve-cells, are not signs of any one definite disease, but are merely indicative of some more or less chronic degenerative condition. Before summing up the matter as to whether the Spanish Town cases may or may not be acute pellagra, I may quote the general résumé of Singer and Pollock on their own findings in the latter condition:

'The one feature which seems to bear the most definite relation to the acute pellagra attack is the axonal change of particular nerve-cells already discussed. With this is probably to be related the scattered Marchi degeneration found throughout the nervous system. This particular picture of widespread axonal chromatolysis with

special involvement of the Betz cells and those of Clarke's column has been noted by all workers upon pellagra with modern methods of staining (Marinesco, Babes, Lugardo, Anderson and Spiller, Kozowski, and others). As has already been noted by one of us, this picture is identical with that described by Meyer as central neuritis. In a personal communication this author assures us that none of his cases presented clinically a picture of pellagra. Attention may also be drawn, in this connection, to the publications upon this syndrome, and upon the cytology of the brain in mental disorders by Southard, Corist, Cotton, Somers, Orr and Coles. In a case of chronic alcoholism recently studied by us, there was, clinically and pathologically, a picture of central neuritis and yet nothing to suggest a history of pellagra. As a matter of fact it would be impossible to distinguish microscopically between the specimens of this case and those here described. We must therefore conclude that pellagra is not capable of recognition post-mortem, apart from the presence of the typical lesions. This is contrary to the opinion expressed by Kozowski in his very detailed report of cases with an excellent digest of the literature.

'The interpretation of these facts is possible only in one way, namely, that such a picture as that presented in central neuritis is a mode of reaction to some harmful agent circulating in the blood, acting upon the axis-cylinder process of the neurons somewhere in their course. Further, it seems clear that this change may be brought about by various ultimate causes, although it is conceivable that the actual excitant of the reaction is the same in all and a product of body metabolism under morbid conditions.

'Besides these acute changes we have also demonstrated the presence of more chronic nerve-cells and glia changes (chronic Nissl change, pigmentary changes, satellitosis, and the presence of an increased number of astrocytes, many of which show various forms of change), which indicate the existence of more chronic type of reaction. That this is an active state at time of death is shown by the presence of ameboid glia cells.

'These changes also differ from the axonal reaction in that they suggest a direct, or primary, action upon the nerve-cells. It is very difficult to determine the exact relationship of these changes to pellagra, but since they are apparently constant, even in the interval

cases (these, however, are not uncomplicated), it seems possible that there is a more chronic degenerative and toxic basis, interrupted at intervals by more acute exacerbations. A study of uncomplicated cases of pellagra dying during a free interval would be necessary in order to throw much light upon this problem.

'We do, however, feel justified from the facts here recorded in drawing the conclusions that pellagra is accompanied during the exacerbations by a generalised intoxication, and that there is nothing specific in the histologic picture presented.

#### 'CONCLUSIONS

'1. Pellagra is accompanied by a general intoxication during the acute exacerbations.

'2. In common with other intoxicative conditions pellagra gives rise to a "central neuritis" reaction.

'3. Some of the changes are characteristic of this particular form of intoxication.

'4. There is no evidence of a local infection of the nervous system.'

Finally, then, as regards the possibility of the Spanish Town cases being pellagrous: Pellagra sine pellagra can, one supposes, occur, though the diagnosis of such must be more of the nature of a lucky conjecture than a certainty. Taking it as a general working rule in pellagra that the sequence of events is usually gastrointestinal symptoms first, cutaneous manifestations second, nervous and mental symptoms third, nevertheless there is no doubt that the order is not by any means invariable, for sometimes the skin manifestations may be the first recognized, while again, in a smaller number, the nervous and mental symptoms appear to precede the others. Close questioning, however, will often reveal the fact that symptoms, possibly quite mild, had occurred one or more years previously.

Against the view of this condition belonging to such a category of pellagra sine pellagra with nervous symptoms as the primary manifestation are the facts that none of the patients exhibited any mental aberration whatever, that in one only was any skin affection present at all, and that was constituted merely by a loss of

pigmentation at the lower end of one radius around an old scar. In none of the other cases, and they totalled fully a hundred, was any cutaneous manifestation found, pellagrous or otherwise, and it is, to say the least, extremely unlikely that there should be a sudden outbreak of pellagra sine pellagra affecting so large a number of persons.

## 2. *Is the disease Beri-beri?*

We may take for the purposes of this part of our discussion the definition of beri-beri as given by Vedder (1913):—

‘Beri-beri is an acute or chronic disease, characterised by changes in the nervous system and particularly by a multiple peripheral neuritis, with an especial tendency to attack the nerves of the limbs, the pneumogastric and phrenics. Ordinarily the clinical picture of a peripheral neuritis is combined in varying degrees with cardiac disturbances, oedema, serous effusion, and gastro-intestinal derangements. Exceptionally cases occur in which cardiac dilatation and sudden death are the first symptoms observed. It is a disease resulting from faulty metabolism, usually only seen in those persons who eat rice as a staple article of diet, and is directly caused by the deficiency of certain vitamins in the food.’

Vedder also states (p. 303) that ‘peripheral neuritis *per se* cannot be the essential lesion in beri-beri, because degeneration of the nerves occurs before symptoms arise, because advanced degeneration may be present accompanied by no symptoms at all, and because degeneration of the nerves remains long after recovery has occurred.’

To resume. Firstly, as regards the symptoms: Whether we consider that the degeneration and paralysis of the muscles affected are the direct result of the neuritis, or whether we take it that the peripheral neuritis *per se* cannot be the essential lesion in beri-beri, it is an established fact that there is a certain predilection for certain muscles to be affected in this disease, and not all the muscles of a limb.

In the Spanish Town cases, on the contrary, it has been definitely stated that there was never seen any wasting of groups of muscles,

and until late no muscular atrophy at all, but as the disease was tending towards a fatal issue a general emaciation came on.

In fact, the motor system was not affected, to any extent at least, in any of the Spanish Town cases, and there was no appreciable loss of power in the muscular movements, even comparatively late in the disease, in fact not until general weakness and exhaustion supervened. With respect to other muscular symptoms, in none of my cases was there seen either contraction of muscles, painful cramps, tonic convulsions or fibrillary twitching, any and all of which may occur in beri-beri; moreover, there was no indication of the reaction of degeneration.

The two conditions agree in that the deeper reflexes tend to disappear early. In beri-beri there may be an exaggeration of the knee-jerk during the first week or so, and this has its counterpart in the case of M. H. of my series; while the superficial reflexes are normal.

Again, in beri-beri ataxia is not usually present; there may be, it is true there is, instability, but it is due to muscular weakness and not to incoordination. The anaesthesia, to take another symptom, in beri-beri most commonly starts over the tibiae, thence passing over the inner surface of the legs and calves and on to the dorsum of the foot, the wrists perhaps being affected at the same time, whereas in the Spanish Town cases invariably the condition started in the toes and soles of the feet, and extended gradually upwards, and later, if the upper extremities became involved at all, it was always in the tips of the fingers that the numbness was first noticed.

Other sensory symptoms are usually present in beri-beri which were never found in the disease at Spanish Town; for example, tenderness of the muscles, especially of the calves on pressure, is complained of in almost all cases, so that patients object and shrink from the muscle-pressure test in beri-beri; this did not occur once in all my cases, nor did any of them exhibit the circumoral anaesthetic area which is found in a certain number at least of beri-beri cases.

Passing on to the other symptoms; in beri-beri cardiac symptoms are nearly always present at some time or other in the course of the disease, such, for example, as palpitation, dyspnoea, increased action, pulsation in the neck, precordium, or upper part of the abdomen; an increase in the area of cardiac dulness, a tendency to oedema of

the lungs. Not one of these symptoms declared itself in the Spanish Town cases, and their absence can hardly be satisfactorily explained by saying that all cases (more than a hundred) were probably the 'dry form' of beri-beri.

Secondly, turning for a moment to the pathological conditions; in beri-beri, though the changes in the spinal cord may be fairly generally distributed, they may be but slight, in fact, the findings never seem to be so marked as those described in the section on the morbid histology of the tissues taken from the Spanish Town patients. Although we may agree that 'dry or paralytic beri-beri is caused by a defective metabolism resulting in more or less degeneration of the entire nervous system,' as Vedder states, nevertheless, personally, I have never seen the changes in the central nervous system in a case of beri-beri so much 'more' as to equal even the least of those present in the fatal Spanish Town cases.

A few words as to the blood conditions, for these do in a measure resemble one another. Though varied results have been reported by different authors, the present decision appears to be that in beri-beri there is not much change in the red cells, not more than might be expected in any serious disease, and that there is nothing characteristic in the differential leucocyte count, but that the Arneth count may be characterized by a slight shift to the right, Classes IV and V constituting some 34 per cent. of the whole.

In none of my cases was the latter seen, the highest being 21·3 per cent. and the majority about 15 per cent.

To sum up this part of our discussion, then, we may say that in spite of a few superficial resemblances, the weight of evidence against the beri-beri idea is overwhelming. In no case was there any oedema at all, nor any palpitation, or dyspnoea, in fact no heart symptoms or physical signs; in no case was there any tenderness of muscles, nor any true paralysis, no distinct foot-drop, no wrist-drop; the site of origin and direction of spread of the anaesthesia was different; in none was there any circumoral anaesthesia; the cord changes, as revealed in the central nervous tissues taken just after death, were most extensive and profound; and, lastly, rice, if it entered into the diet of these patients at all, did not constitute a regular or large part of it.



The next point to be taken up in our discussion is :

3. *What relation, if any, does the Spanish Town outbreak bear to the so-called Peripheral Neuritis of Jamaica?*

The first records that I can trace concerning this so-called peripheral neuritis, which is a very common condition in Jamaica, are articles by Dr. H. Strachan (1888 and 1897). The author of these was then Senior Medical Officer in Jamaica, and, as these articles show, a man of keen observation.

On reading his articles by the light of present-day knowledge, one sees that he has included cases with skin lesions and pigmentation which would now be regarded as pellagra, and other patients exhibiting local paralyses and muscular atrophies, which are not observed in those cases relegated at the present day to the category of this obscure peripheral neuritis.

The symptoms of a patient suffering from the so-called peripheral neuritis are as follows:—He has usually been ill for a long time, weeks, months, perhaps a year or two, and does not remember the nature of the onset in most cases. At the time when he presents himself at the hospital the chief complaints are numbness and cramps in the feet and hands, dimness of vision, and hardness of hearing. If the illness is of shorter duration, there is slight excoriation at the edges of the eyelids and margins of the lips, and the palpebral conjunctiva is hyperaemic. The degree of impairment of vision is very variable, it may be a mere dimness, or it may be such that the patient cannot count fingers, and may not be able to recognize his friends by sight. The deafness also may vary from merely a little 'hardness of hearing' to complete inability to hear at all.

'Sensation is blunted, but never completely abolished,' says Dr. Strachan. 'It is the numbness and tingling, or "crampiness" which the patient first notices . . . and which, if he be of a superior grade of intelligence, leads him to seek advice; if he be not, or be careless, it is the gradually increasing impairment of vision which brings him to the doctor.'

'There is,' he states in another place (p. 478), 'no alteration in the reaction of the pupil to light and accommodation, no falling when the eyes are closed, and the sphincters will not be affected.'

He mentions that in very grave cases 'the innervation of the diaphragm and of the heart is seriously involved . . . and leads to a fatal termination.' Here, I feel sure, he was meeting with beri-beri neuritis amongst the number.

He says again (p. 482), that 'redness and irritation of the eyelids and lips are often the first external signs noticed. It soon passes into a slight eczematous condition, especially at the corners of the mouth.'

Strachan thinks that the cause is malaria; he states 'as to the poison which, circulating in the blood of the affected person, causes this form of peripheral neuritis, I have been led to think that it is the poison of malaria.'

At the present day, particularly in certain parts of the country, many of these so-called peripheral neuritis cases may be met with, some going about, some in the hospitals, some in the Poorhouses. Those able to move about complain chiefly of 'dark sight,' which they interpret as inability to sew or read, or, in advanced cases such as one finds in institutions, inability to count fingers or recognize faces; they are nearly always partially deaf, in some cases quite deaf; those who can walk do so with a kind of 'steppage gait,' but without real drop-foot, and not with a tabetic stamp, nor on a wide base. They exhibit little, if any, loss of power until they become bedridden and emaciated, and at no time do they show any localized wasting of muscles or muscle-groups; the sphincters are never involved, the pupils react normally to light and accommodation; shutting the eyes does not increase the ataxia, the knee-jerks are absent.

Lieut.-Col. W. S. Harrison, R.A.M.C., when in Jamaica in 1914, made some brief notes on cases seen by him, and he states: 'The legs are always much more affected than the arms. Dimness of vision is a constant and early feature and may amount to almost blindness; deafness is also all but invariable, and the amount of it seems to vary with the severity of the disease. In some improvement may occur so that the patients are able to get about with a very ataxic, high-stepping gait, and then the condition comes to a standstill. Cases in the Almshouse have been there for six or more years with practically no alteration for four or more years.'

'Girdle pains are much more frequent in the early stages.'

He describes one chronic case which terminated fatally; the man

gave a history of the onset as 'fairly sudden with tingling and numbness in the feet, rapidly extending in the legs and to the arms, and he had been in this condition for at least six months.'

He noted particularly that 'there is comparatively little wasting of the muscles considering that the symptoms seem to point to a neuritis, but this is a constant feature of these cases. This man's legs were no more wasted than one would expect to see them in a man who had lain for six months in bed. There were no deformities from contractures, there were no skin lesions, the knee-jerks were absent, and the plantar reflex present, although the patient told me that he could not feel when I touched the sole of the foot.'

Harrison made the following general note after seeing a large number of cases which were got together for him as typical cases of peripheral neuritis. 'There were no children among the number. Paralysis varied a good deal in different cases, from a slight ataxia to complete inability to move the legs; in no case were the arms more severely affected than the legs, and, as a rule, it was only the legs which were seriously affected, although the patient complained of the numbness in the hands and that they often dropped things. The cases were of varying durations; some of the older ones having been disabled for ten years; deformities were conspicuously absent, while in no case was there any marked wasting of the affected limbs.'

After these more general statements he briefly quotes the following two cases: 'A young man, aged 27, who had been ill since Easter (about two months); the illness commenced with numbness of the feet, but he had had "soreness" of the eyes for some time before and gradually increasing dimness of vision. There had been no particular pain at any time, and no trouble in the arms. The eyes were now better, but the legs were getting worse and there were cramps in the feet. There was some deafness, but this was not very marked. Patient said he was now (May 29th) beginning to get "cramps and burning" in the hands. There was no loss of sensation, no atrophy of muscles, which appeared to be rather ataxic than actually paralysed. The wife of this man was also commencing to suffer from dimness of vision and burning of the soles of the feet, but no deafness so far, and walks all right, though soon tired. Knee-jerks absent.'

I have quoted this last note fully because it appears to me to

compare, even in many small details, with the cases of the Spanish Town epidemic, and during the last few months I have made a point of seeing cases of 'peripheral neuritis' when the opportunity arose, and the condition in practically all was that described above—numbness of feet and legs and difficulty in walking, slight deafness and 'dark sight,' numbness in some cases of fingers, with inability to sew and a tendency to drop things, and on examination absence of knee-jerks, retention of superficial reflexes, no objectively discoverable change in sensation, except in some a difficulty in distinguishing heat from cold; an ataxic gait, often steppage, but not tabetic, and without atrophy of muscles.

These patients may live for many years and die from some intercurrent disease, so I have not yet had an opportunity of examining the tissues post-mortem.

As a rule the patients have been so long ill that they have forgotten the actual symptoms at the time of onset; the numbness and ataxia remaining are most impressed upon them, and thus they come to regard these as the first symptoms. If, however, the memory is sufficiently good, or if the disease has not been so long continued, questioning as to eye and mouth symptoms will often bring out the fact that these did precede the actual nerve symptoms, as in the cases recorded above by Harrison. In my opinion there is strong evidence to show that the Spanish Town cases were examples of the acute form or acute stages of the condition which has for years been called in Jamaica 'Peripheral Neuritis,' and I feel sure that the elucidation of the cause of the former will also clear up the mystery of the latter.

#### 4. *Is the condition a new 'Deficiency' disease?*

The suggestion has been made on more than one occasion to attribute 'peripheral neuritis' to some diet deficiency, more so, naturally, since beri-beri has been shown to be so caused.

Such a suggestion, unsupported by any evidence, merely serves to cloak our ignorance and to baffle investigation.

The chief argument brought forward in support of the theory is that analyses of the articles of diet used by the natives in Jamaica show a relative deficiency in protein and excess of carbohydrates, and this is backed up by analyses of the constituents of the dietaries supplied in institutions in which these cases are found. These arguments, however, will not bear examination. In the first place

these articles of diet are in use by the generality of the people (I refer to the poorer natives) from infancy upwards and at all seasons, nevertheless children and young adults are not affected, but the labouring class. Secondly, the initial symptoms seem to declare themselves at certain seasons, namely, at the time of cutting and carrying of the cane crop, and during this time little if any of the usually employed native foods are eaten at all. Several overseers have told me that the labourers come to work without any breakfast because they cut cane for themselves as soon as they get to the fields and eat it for breakfast, and they eat it all day long, and take practically nothing else while the crop is on. Thirdly, analyses of the dietaries in the public institutions where cases of peripheral neuritis are found have no weight, because these cases do not *arise* in such institutions, but outside, and they come into them only when they are no longer able to work and support themselves; moreover, those patients who are only mildly affected and get well, and, in fact, any who show improvement at all, do so on these very diets which are impugned.

The analogy, therefore, which some practitioners here bring forward that beri-beri is a deficiency disease, and occurs in epidemics (such as that in Bilibid Prison, Manila, in 1901-2), and that this peripheral neuritis is similar, is a false analogy altogether, for the epidemic here did not arise in any institution but among healthy labourers on sugar estates in the neighbourhood of Spanish Town, and these were attacked suddenly while at work.

Catto in his last report (1916), when mentioning 'peripheral neuritis,' gives analyses to show that 'with the exception of peas and beans all the native products are strikingly deficient in protein substances.' He mentions in connection with this the diets used at the Kingston and St. Andrew Union Poor House, and in support of the disease being a deficiency one quotes Koch and Voegtlin, saying that 'a diet deficient—even comparatively—in protein constituents, though rich in carbohydrates, causes in the more highly organised mammals a very marked disturbance in the metabolism of the elements composing the nervous system.' And, again, in his conclusions, 'this restricted diet is of a nature likely to produce detrimental effects in the human organism, especially on the nervous system.'

Apparently, then, we are asked to believe that because (1) a diet

deficient in protein constituents causes a disturbance in the metabolism of the elements composing the nervous system, and because (2) the native products, except peas and beans, are deficient in protein substances, and because (3) cases of peripheral neuritis show changes in the nervous system, therefore peripheral neuritis is due to the native diet.

I may mention also that in the same report Catto quotes a statement made to him by the medical officer in charge of the Poor House, the diet of which institution he has given, saying: 'Some are admitted with very marked nervous symptoms; quite unable to stand. After some months they are able to walk with the aid of crutches; gradually they discard these and use an ordinary walking-stick. Usually a considerable amount of shakiness of the lower limbs persists. In less advanced cases the patients complain of numbness or cramps in feet and hands, and a great heat about the body, especially in the back. Frequently the condition subsides after several months' treatment.' All this, be it noted, on the incriminated diet!

'In other cases the patients are admitted in a bedridden condition and never leave their beds, gradually sinking and dying from inanition.' 'Diarrhoea is the immediate cause of death in some cases.' Compare this last statement with the histories of the fatal Spanish Town cases.

As a minor point one might add that if these Spanish Town cases are to be ascribed, as the practitioners, in charge of them do, to poverty and inadequate food, that is, to a food deficiency, why should there be the same history of onset in each, an acute origin with eye and mouth symptoms? Moreover, as stated in those histories, the patients were by no means all poor, and many stated that they were getting plenty to eat.

##### 5. *Is the condition microbial in origin?*

To the discussion of this point I fear I have only negative evidence to put forward:

1. Careful examination and cultural experiments were made from the discharges, the abrasions, and the lesions generally of the eyes and mouth, where the first lesions appeared to be, but nothing beyond the ordinary air and mouth organisms were isolated. One

must not conclude, of course, that some organism may not have started the condition and then have disappeared.

2. Cultures of the blood were made at various periods of the illness, but all remained sterile, both aerobic and anaerobic.

3. Cultures of the cerebro-spinal fluid made on various media at various periods from the earliest to the latest, and even just after death, have all remained sterile.

4. Cultures of the urine and faeces have yielded only disappointing results; very rarely was any organism isolated which is not to be found in normal faeces.

5. In none of the tissues taken at the autopsies, and practically every tissue in the body was taken and stained in various ways to show the presence of organisms—both bacterial and protozoal—was any organism detected. Levaditi's method was carried out on all the nervous tissues as well as others, but no treponemata or such-like organisms were seen.

6. The results of the detailed blood examinations already given in Section IV are not such as would lend support to the probability of any bacterium being the cause, while the uniformly negative results of blood culture and the uniform absence of organisms from the sections prove at least that the condition is not a bacteriaemia. As to whether it may be ascribed to a bacterial toxin will next be discussed.

#### 6. *Is the condition due to an Intoxication?*

Obviously, until a definite toxin has been found, which, introduced in a pure state, will produce the symptoms of this disease, any positive assertion that the condition resulted from an intoxication would be premature. Nevertheless, it would appear that an 'Intoxication theory' will best fit the facts, so far as they are known at present.

Taking first the question of the food of those who were attacked. At ordinary times, as has been already stated, the food of the native consists of yam, breadfruit, cocoa, peas, beans, cornmeal, salt-fish, and so on. At the time of this epidemic those who were attacked were working in the cane-fields, and during this period of cutting and carrying cane the labourers live almost exclusively on the canes. Many of the natives also, when not actually working

in the cane-fields, live largely on the sugar cane if they can procure it.

Let us presume for a moment that the canes are at fault, and see what can be urged on both sides. Many of the labourers under similar circumstances, working on the same estates, also ate cane and did not suffer. This point is not an insuperable one; firstly, those who escaped may not have been working there long enough, just as beri-beri may take ninety days to develop on a diet of milled rice. Secondly, canes are eaten largely on other estates and in other countries, but such epidemics have not, to my knowledge, been encountered, or, at all events, reported before, and they are certainly far too striking and serious to be overlooked.

The evidence against the sugar-cane itself—the ordinary healthy cane—amounts to practically nothing, but what about the possibility of something in or on the canes affecting only a certain proportion of them?

This idea started a further train of enquiries, and I am informed that sore mouth is not uncommon in cane workers and cane eaters. Apparently this is not due, at all events in the majority, to wounds caused by the cane fibres, nor to any acidity of the juice.

The top part of the cane contains very little sugar; this is cut off before the canes are carted to the factory, or before the person eats any of the cane, or he may break it off with his hands. This top part which is cut or torn off is surrounded by a fine hair-like growth, almost like a powder or fine dust. In some Barbadoes canes these hairs are larger and more irritating, and on this estate near Spanish Town there is, I am told, a larger proportion of these canes than on other estates. This fact is mentioned incidentally; it may have nothing to do with the case. These hairs stick to the fingers and are distinctly irritating, and it is these which appear to cause the sore mouth. The irritation produced by handling the canes is a well-recognised thing, so much so that many of the labourers wear protective covering on the hands and forearms while at work in the fields.

It would be quite a plausible explanation to suggest that in the cutting, and still more in breaking off these tops, the hands become covered with these particles, especially when the labourers are perspiring in the heat of the day. From the hands they would



then be conveyed to the eyes, as when wiping the perspiration from their faces, or to their mouths when eating. The more delicate conjunctival mucous membrane would react more rapidly than the oral, and thus might be explained the 'itching and burning' of the eyes being the first symptom and the sore mouth the next.

Two possibilities now arise, in fact three, but the one can be put out of court very briefly. These possibilities are:—

1. Are these particles themselves the source of a toxin?
2. Are the sores produced the first lesion, as actually part of the disease?
3. Do the sores merely act as a favourable site at which an organism may enter and multiply, or at which a poison may be introduced?

1. *Are the particles themselves the source of the toxin?*

This question, in my opinion, can be ruled out for the following reason. These particles are on every sucker, and if they were the *causa causans* hardly a single labourer on the estates could escape. Cases of sore eyes, sore mouth, and 'peripheral neuritis' are fairly common, but if the above were true they would be almost universal in cane districts.

2. *Whether the sore eyes constitute the primary lesion proper of the disease cannot be stated decisively at present.*

In favour of the positive is the fact that the sequence was, with one exception, the same; 'itching and sore eyes' followed by 'soreness of the mouth'; whereas almost, if not quite as potent an argument against it, is the fact that the eyelids were just as likely to be the first to come into contact with infected fingers when the perspiration was being wiped away from the eyes when the labourers were working under a tropical sun.

3. *As regards the last:*

Such open sores would form an ideal site for the development of organisms. The reasons against the condition being bacterial have already been given, but those arguments apply mainly against the bacteriaemic idea; it is possible that organisms might settle there, and produce their poison which would be absorbed from such an extensive raw surface, just as the diphtheria toxin from a local growth of the Klebs-Löffler bacillus, and like the latter be able to

produce severe nerve lesions, which may leave residual symptoms. The poison in the Spanish Town cases, judging from the post-mortem findings, so affected the nerve tissues as to show clearly the reason why complete recovery is so rare.

Lastly, it is quite plausible to regard the eye and mouth symptoms as being set up by the irritation, as already mentioned, and the other conditions, intestinal and nervous, as due to some ingested toxin, comparable, for example, to ergotism. Such a theory would account for the initial symptoms of sore eyes and mouth and for the two sub-divisions of cases later, those with intestinal symptoms corresponding to the irritation of acute ergotism, and due to local action, and those with later development of nervous symptoms when the poison is absorbed. I do not mean to imply that the poison itself has an action like that of ergot, but merely the analogy of a foreign growth producing intestinal and nervous symptoms.

All that we are justified in saying in our present state of knowledge is that the history, course, and post-mortem findings in the Spanish Town epidemic and in the (wrongly) so-called peripheral neuritis cases indicate that the condition is that of a 'Central Neuritis' due to some toxin, possibly microbial, more probably not, affecting mainly workers on sugar estates, and, again, possibly due to the growth of some fungus or parasite upon the suckers, tops or leaves, of the canes.

### VIII. SUMMARY

1. A certain epidemic broke out in the earlier months of 1917 among the labourers on a sugar estate in Jamaica.
2. The onset in each case was sudden, the patients being attacked while at work and apparently in good health.
3. The initial symptoms in all cases were conjunctivitis and stomatitis.
4. Thereafter the patients could be readily divided into two categories: (i) with intestinal symptoms; (ii) with nervous symptoms.
5. The diet of those affected consisted exclusively, or almost exclusively, of sugar-cane.
6. The cane-tops, which are cut or broken off, are covered with

small hairs which are very irritating and may have set up the original conjunctivitis and stomatitis, and, when swallowed, the subsequent diarrhoea.

7. Fresh cases ceased with the cessation of the crop or almost immediately after.

8. No case with early diarrhoea exhibited any affection of the nervous system.

9. Nervous system cases were always constipated until the final two or three days before death.

10. Wassermann reactions with both the blood-serum and the cerebro-spinal fluid were invariably negative.

11. Blood examinations reveal very little abnormality as regards total counts; differential leucocyte counts showed in all cases a marked relative lymphocytosis.

12. Arneth index was very little different from what is found normally in natives in the tropics.

13. The morbid anatomy of the nervous cases is typical of a 'Central Neuritis.'

14. There is no reason for thinking that the disease is pellagral in nature, or has any relation with pellagra.

15. There is no reason for regarding it as beri-beri.

16. There are many contraindications to the condition being a new form of 'deficiency disease.'

17. There is every reason for considering these cases as representing the acute form, or acute stage, of what has for many years been erroneously spoken of as 'Peripheral Neuritis' in Jamaica.

18. There is no positive evidence that the disease is microbial in origin, at least not a bacteriaemia.

19. All the signs and symptoms tend to point to its being a condition of '*Intoxication*.'

December, 1917.

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## Summary of Blo

A = Ankylostome. a = Ascaris. T = Trichiuris. M = Mala

No.	Initials	Character of Case	Stage of disease	Polymorphonuclear neutrophil	Promyelocyte	Myelocyte	Metamyelocyte	Eosinophile
1	D. J.	Mild, intestinal ... ..	Height ... ..	% 54.4	% ...	% 1.0	% 0.2	% ...
2	"	" ... ..	" ... ..	43.0	0.2	1.2	...	0.
3	"	" ... ..	Nearly recovered ... ..	36.6	0.4	0.8	0.6	0.
4	J. S.	" ... ..	Early ... ..	46.4	1.2	2.2	1.0	...
5	"	" ... ..	Height ... ..	47.2	0.6	2.8	1.6	...
6	J. A.	Severe, intestinal ... ..	" ... ..	56.6	1.0	1.2	1.2	...
7	E. S.	Average nervous, recovery ...	" ... ..	27.2	0.8	0.8	0.6	...
8	V. McC.	" ... ..	Nearly recovered ... ..	37.4	0.8	1.6	1.2	...
9	A. B.	Moderately severe nervous ...	Recovering ... ..	33.8	0.8	1.2	1.0	...
10	E. M.	Severe nervous ... ..	Height ... ..	37.4	0.4	1.6	0.6	...
11	"	" ... ..	Same condition ... ..	41.2	0.4	0.8	0.6	...
12	C. S.	" ... ..	Height ... ..	43.0	0.2	0.8	0.8	...
13	R. H.	" ... ..	Improving ... ..	30.6	0.4	0.8	0.2	...
14	E. G.	Severe and chronic nervous ...	Near height ... ..	37.8	0.6	2.0	0.8	0.
15	"	" ... ..	Height ... ..	46.4	0.8	2.4	1.6	0.
16	"	" ... ..	Chronic ... ..	49.0	0.8	1.4	1.2	...
17	C. H.	" ... ..	Slight improvement after height	48.2	0.6	1.4	1.4	...
18	A. D.	Severe nervous, probably fatal ...	Height ... ..	52.8	1.4	1.0	1.0	...
19	J. P.	Severe, fatal, nervous ... ..	Early ... ..	45.0	0.4	0.6	1.0	...
20	"	" ... ..	Height ... ..	41.0	0.6	1.4	0.2	0.
21	"	" ... ..	In extremis ... ..	64.0	1.0	1.2	...	...
22	G. P.	" ... ..	Near height ... ..	47.8	0.2	0.2	0.8	...
23	"	" ... ..	Near end ... ..	67.0	0.2	0.8	...	...
24	T. J.	" ... ..	At height ... ..	49.8	0.2	0.4	0.8	...
25	"	" ... ..	In extremis ... ..	54.6	0.8	0.6	1.0	...
26	M. H.	" ... ..	Near height ... ..	60.4	0.2	0.6	0.2	...
27	J. N.	Very chronic; see case ... ..	Stationary ... ..	41.6	0.6	1.8	0.4	...
28	S. C. T.	" ... ..	" ... ..	37.6	0.8	0.4	0.2	...

aminations.

= Amœba of Dysentery. Pyocy. = *B. pyocyaneus*.

Eosinophile	Basophile	Large Mononuclear	Transitional	Large Lymphocyte	Small Lymphocyte	Türk's cells	Rieder cells	Arneth Count						Arneth Index		
								I	II	III	IV	V	Stabker-nige	I and II	I, II and half III	
0.8	0.4	1.0	0.6	4.6	32.8	...	1.2	9.9	40.4	32.4	12.2	2.2	2.9	50.3	66.5	A. a. T.
2	0.8	3.6	1.6	7.6	29.8	1.0	1.6	3.7	36.4	35.3	13.9	3.2	7.5	40.1	57.7	
8	2.4	4.8	3.8	7.4	30.4	0.2	2.4	6.5	37.1	32.2	13.8	3.6	6.8	43.6	59.7	
2	1.4	4.0	2.4	5.4	30.8	0.8	2.2	15.1	44.4	25.8	8.2	2.2	4.3	59.5	72.4	M. D. Pyocy.
4	1.2	3.6	0.8	6.0	31.4	1.0	3.4	13.6	50.4	22.0	7.6	1.3	5.1	64.0	75.0	
2	1.8	3.0	2.2	6.2	21.2	0.6	1.8	17.0	40.9	25.5	7.4	5.0	4.2	57.9	70.6	
0	0.6	3.2	1.6	7.4	49.8	...	3.0	6.6	38.9	29.5	16.9	4.4	3.7	45.5	60.2	A. T.
2	0.4	4.6	2.8	7.2	33.8	1.8	0.2	6.4	42.8	38.0	4.8	1.1	6.9	49.2	68.2	A.
0	0.6	6.6	4.6	9.2	21.8	1.8	0.6	3.0	39.1	37.3	11.8	3.5	5.3	42.1	60.7	M. A.
2	0.6	4.6	1.8	9.8	35.6	1.0	2.4	9.1	53.0	21.4	9.6	3.2	3.7	62.1	72.8	
0	1.2	3.8	2.8	8.4	33.2	1.6	2.0	5.8	47.1	35.4	7.8	1.5	2.4	52.9	70.6	
0	1.8	3.6	2.4	11.6	29.6	1.4	0.8	6.5	42.3	25.6	13.0	3.7	8.9	48.8	61.6	
4	0.4	2.2	1.0	8.6	39.0	1.0	0.4	6.6	45.7	27.5	12.4	1.9	5.9	52.3	66.05	A. a.
0	1.8	3.4	3.4	9.8	28.4	0.4	1.2	5.8	48.7	31.2	5.3	2.6	6.4	54.5	71.1	A.
4	0.8	4.6	3.4	10.2	18.0	2.6	0.6	8.2	46.1	28.9	7.3	3.5	6.0	54.3	68.7	
8	0.2	4.2	2.2	7.0	26.2	1.2	0.8	11.4	58.0	19.2	2.0	1.6	7.8	69.4	79.0	
2	1.6	2.4	3.2	9.6	24.6	3.4	0.4	8.7	46.5	30.3	7.0	4.6	2.9	55.2	70.8	
0	0.6	2.6	1.6	7.6	28.2	1.0	0.2	10.3	42.0	29.9	11.0	3.4	3.4	52.3	67.2	A. a.
0	0.6	2.6	2.2	7.4	35.2	1.0	...	4.5	33.8	40.0	12.5	5.4	3.8	38.3	58.3	A.
2	0.8	2.2	1.8	5.4	35.8	2.8	0.4	6.8	36.6	36.1	12.7	3.4	4.4	45.4	61.4	
8	1.0	3.2	2.6	3.2	14.6	2.2	0.2	6.6	43.1	30.6	9.7	6.9	3.1	49.7	65.0	
4	0.4	3.2	3.6	9.6	28.8	2.6	1.4	5.4	38.5	35.6	12.9	5.5	2.1	43.9	61.7	
0	1.0	3.4	1.2	4.6	17.8	2.0	...	7.7	43.0	33.4	9.6	4.8	1.5	50.7	67.4	
0	1.2	2.0	2.0	6.2	32.2	1.8	0.4	8.4	53.4	24.6	8.4	2.4	2.8	61.8	74.1	A. a.
8	1.4	2.4	2.2	5.0	25.0	1.2	1.0	8.7	54.6	23.9	8.1	1.8	2.9	63.3	75.2	
2	1.2	5.8	3.0	6.6	17.8	0.4	0.6	8.9	46.4	27.5	11.3	3.3	2.6	55.3	69.0	
6	2.0	4.4	2.2	10.8	32.8	1.0	0.8	6.3	35.1	32.7	14.0	6.3	5.6	41.4	57.7	
0	2.2	3.0	4.2	12.0	26.6	1.8	1.0	2.7	26.1	34.0	25.0	5.3	6.9	28.8	45.8	A.

## Summary of Symptoms

N = Normal. + = present. — = absent or unaffected. ? = doubtful. x = variable. ... = not tested.

		D. J.	J. S.	J. A.	C. D.	H. B.	E. S.	V. McC.	A. B.	E. M.
Onset	Intellect ... ..	N	N	N	N	N	N	N	N	N
	Sore eyes ... ..	+	+	+	—	+	+	?	+	+
	Sore mouth ... ..	+	+	+	+	+	—	+	+	+
	Diarrhoea early ... ..	+	+	+	—	—	—	—	—	—
	„ terminal ... ..	—	—	...	+	—	—	—	—	—
Number	Constipation ... ..	—	—	—	+	+	+	+	+	+
	Feet ... ..	—	—	—	+	—	+	+	+	+
	Legs ... ..	—	—	—	+	+	+	+	+	+
	Thighs ... ..	—	—	—	+	—	?	—	+	±
	Hands ... ..	—	—	—	—	—	—	—	+	+
	Arms ... ..	—	—	—	—	—	—	—	—	±
	Tongue ... ..	—	—	—	—	—	—	—	—	—
	Dysarthria ... ..	—	—	—	—	—	—	—	—	—
	Girdle ... ..	—	—	—	...	—	+	—	—	+
	Touch ... ..	—	—	—	...	—	—	—	—	—
Changes in or abnormalities of sensation	Heat and cold ... ..	—	—	—	...	±	...	...	...	—
	Pain ... ..	—	—	—	...	+	?	—	—	—
	Position ... ..	—	—	—	...	—	—	—	—	—
	Joint ... ..	—	—	—	...	—	—	—	—	—
	Muscle pressure ... ..	—	—	—	...	—	—	—	—	—
	Formication ... ..	—	—	—	+	—	—	—	—	—
	Weights ... ..	—	—	—	...	—	—	—	—	—
	Vibration ... ..	—	—	—	...	—	...	—	—	—
	Localisation of sensation ... ..	N	N	N	...	N	N	N	N	?
	Stereognosis ... ..	N	N	N	...	N	N	N	N	?
	Paralysis ... ..	—	—	—	...	—	—	—	—	—
	Atrophy of muscle ... ..	—	—	—	...	—	—	—	—	—

ented.

weakness (in place of 'numbness.')  $\pm$  = affected, but in slight degree only.

S.	R. H.	E. G.	C. H.	A. D.	J. P.	G. P.	T. J.	M. H.	J. M.	J. N.	S. C. T.
N	N	N	N	N	N	N	N	Fair	N	N	N
+	+	+	+	+	+	+	+	+	+	+	-
+	+	+	-	+	+	+	+	+	+	+	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	+	+	+	+	+	-	-
+	+	+	+	+	+	+	+	+	+	+	x
+	+	+	+	+	+	+	+	+	+	+	+w
+	+	+	+	+	+	+	+	+	+	+	+w
-	+	+	+	+	$\pm$	+	-	$\pm$	+	+	-
-	+	+	+	+	+	+	+	+	-	+	+w
-	-	-	-	+	+	+	+	+	-	-	-
-	-	-	-	-	+	+	+	+	-	-	-
-	-	-	-	-	+	+	+	?	-	-	-
+	+	-	-	-	-	-	-	+	-	-	-
-	-	$\pm$	-	-	-	-	-	-	-	-	-
-	+	delay	...	delay	-	+	...	-	-	-	+
-	-	-	+ ?	-	-	-	+ ?	-	-	-	-
-	-	+ ?	-	+	-	+	+	-	+	-	-
-	-	+ ?	-	+	+	$\pm$	+	-	+	-	-
-	-	-	-	- ?	+	-	-	-	-	-	-
-	-	+	+	-	-	-	-	-	-	-	-
...	...	+	...	...	- later +	...	...	...	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
N	N	N	N	N	N	N	N	N	N	N	N
N	...	-	N	...	...	-	?	...	N	N	N
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	general emacia- tion	general emacia- tion	-	-	-	-	-

## Summary of Symptoms

N = Normal. + = present. - = absent or unaffected. ? = doubtful. x = variable. ... = not tested

	D. J.	J. S.	J. A.	C. D.	H. B.	E. S.	V. McC.	A. B.	E. M.	
Gait	Steppage ... ..	-	-	-	...	-	-	-	+	-
	Spastic... ..	-	-	-	...	-	-	-	-	±
	Ataxic ... ..	-	-	-	...	-	+	-	-	-
	Tabetic ... ..	-	-	-	...	-	-	-	-	-
	Not characteristic but abnormal ... ..	-	-	-	...	+	-	-	-	+
Incoordination	Romberg ... ..	-	-	-	...	-	?	-	-	-
	Legs: out of bed ... ..	-	-	-	...	-	+	-	-	+
	in bed ... ..	-	-	-	...	-	-	-	-	±
Pupils	Hands ... ..	-	-	-	...	-	-	-	-	+
	Light reaction ... ..	N	N	N	...	N	N	N	N	N
	Convergence ... ..	N	N	N	...	N	N	slow	N	N
	'Dark Vision' ... ..	-	-	-	...	-	-	+	+	-
	Nystagmus ... ..	-	-	-	...	-	-	-	-	-
Reflexes	Ocular paresis ... ..	-	-	-	...	-	-	-	-	-
	Diplopia ... ..	-	-	-	...	-	-	-	-	-
	Vertigo ... ..	-	-	-	...	-	-	-	-	-
	Deafness ... ..	-	-	-	...	-	-	-	-	-
	Taste ... ..	N	N	N	...	N	N	N	N	N
	Jaw ... ..	N	N	N	...	N	N	N	N	N
	Elbow ... ..	N	N	N	...	N	N	N	N	N
	Wrist ... ..	N	N	N	...	N	N	N	N	?
	Knee ... ..	N	N	N	...	N	-	?	-	-
	Ankle ... ..	N	N	N	...	N	-	?	-	-
	Babinski ... ..	N	N	N	...	N	-	?	?	-
	Superficial ... ..	N	N	N	...	N	x	?	N	x
Sphincters ... ..	N	N	N	...	N	N	?	N	N	
C. S. Fluid ... ..	...	...	N	...	...	...	...	...	N	



-continued.

sented.

= weakness (in place of 'numbness').  $\pm$  = affected, but in slight degree only.

C. S.	R. H.	E. G.	C. H.	A. D.	J. P.	G. P.	T. J.	M. H.	J. M.	J. N.	S. C. T.
+	-	...	...	...	-	-	-	-	-	+	-
-	+	...	...	...	-	-	-	+	+	+	$\pm$
-	-	...	...	...	-	+	+	+	+	-	-
-	-	...	...	...	-	-	-	-	-	-	-
-	-	...	...	...	+	-	-	-	-	-	-
-	-	...	...	...	-	?	-	-	...	-	-
$\pm$	...	+	...	...	+	+	+	+	+	-	-
-	-	$\pm$	+	+	-	-	-	$\pm$	$\pm$	...	...
-	-	+	+	+	+	+	+	+	-	-	-
N	N	N	N	N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	N	N	N	N	N
-	+	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	$\pm$	-	-	-	-	$\pm$	-	-	-	-	-
N	N	N	N	N	N	N	N	N	N	N	N
N	N	N	N	N	N	N	...	N	N	N	N
N	-	N	N	N	?	?	N	N	N	N	N
?	-	?	-	-	-	-	-	N	N	N	N
-	-	-	-	-	-	-	-	+ later -	-	+	+ ?
-	-	-	-	-	-	-	-	+ later -	-	+	...
...	N	...	?	?	...	-	-	?	...	...	?
N	N	N	N ?	N	x	...	...	N	N	N	N
N	N	N	N	N	N	N	N	N	N	N	N
...	...	...	...	...	N	N	N	...	...	...	...

## EXPLANATION OF PLATES

## PLATE II

- Fig. 1. Lumbar enlargement, lower part.  
Fig. 2. Lumbar enlargement, upper part.

## PLATE III

- Fig. 3. Lower dorsal cord.  
Fig. 4. Upper dorsal cord.

## PLATE IV

- Fig. 5. Hypophysis,  $\frac{2}{3}$ -in.  
Fig. 6. Cells of Clarke's column,  $\frac{2}{3}$ -in.

## PLATE V

- Fig. 7. Optic nerve,  $\frac{2}{3}$ -in.  
Fig. 8. Optic nerve,  $\frac{1}{6}$ -in.

## PLATE VI

- Fig. 9. Nerve fibres at posterior root ganglion,  $\frac{1}{6}$ -in.  
Fig. 10. Tibialis anticus,  $\frac{1}{6}$ -in.

## PLATE VII

- Fig. 11. Pancreas,  $\frac{1}{6}$ -in.  
Fig. 12. Liver,  $\frac{1}{6}$ -in.



Fig. 1



Fig. 2



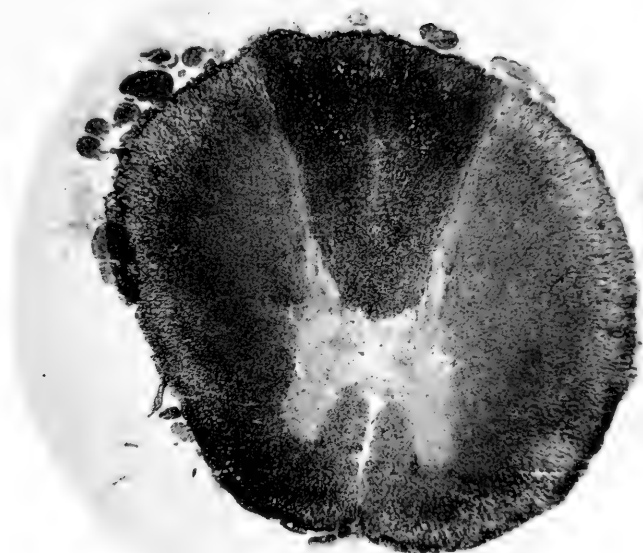


Fig. 3

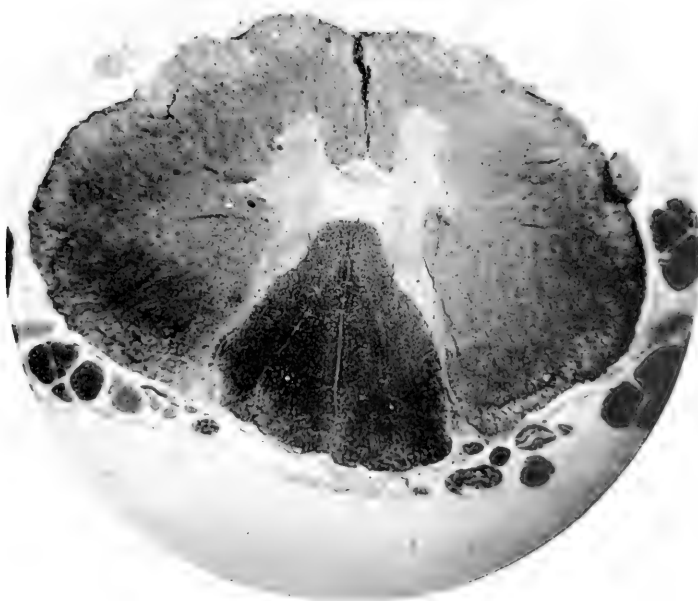


Fig. 4





Fig. 5

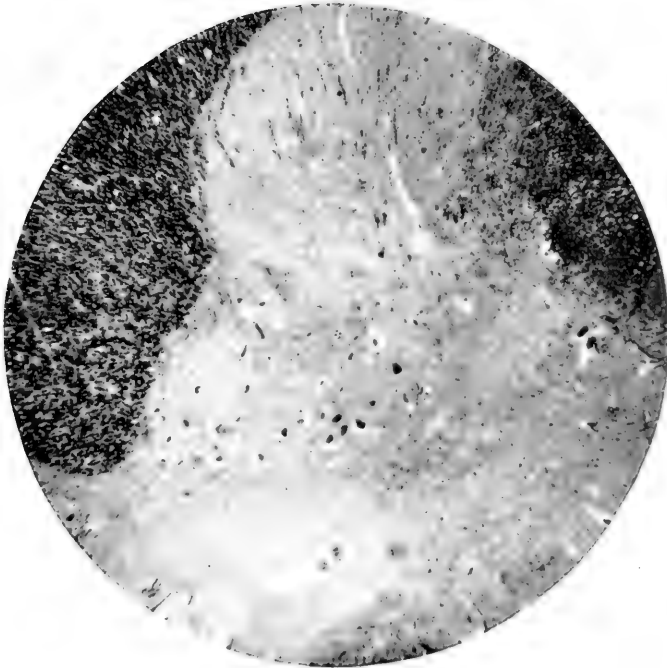


Fig. 6





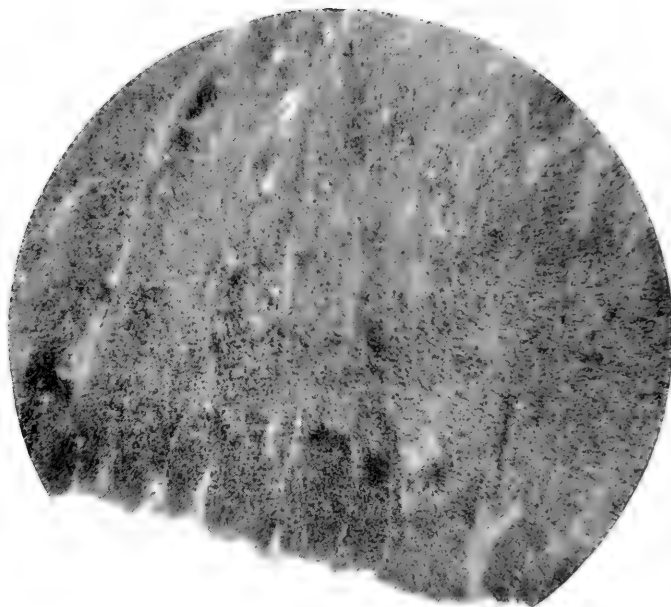


Fig. 7

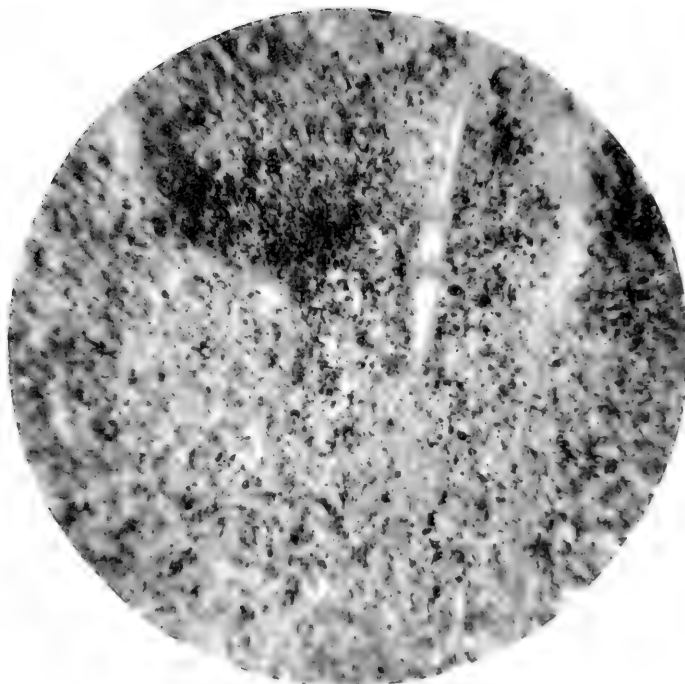


Fig. 8



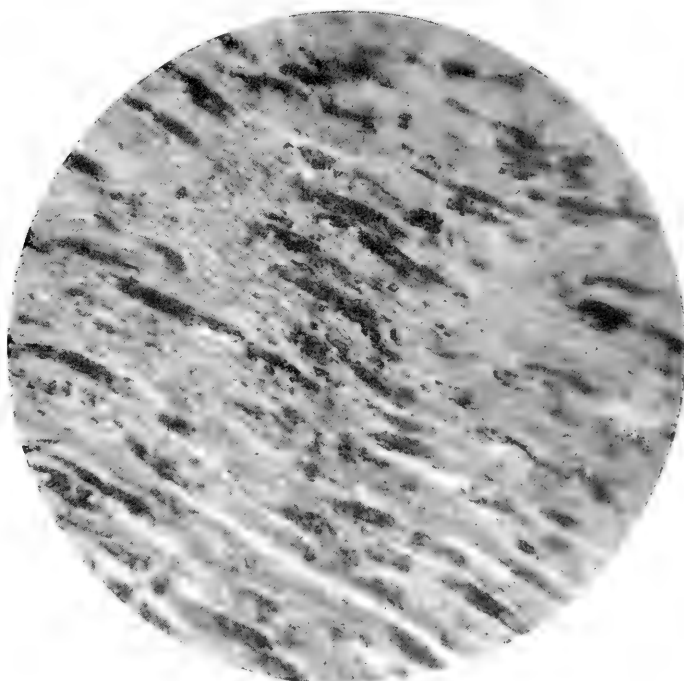
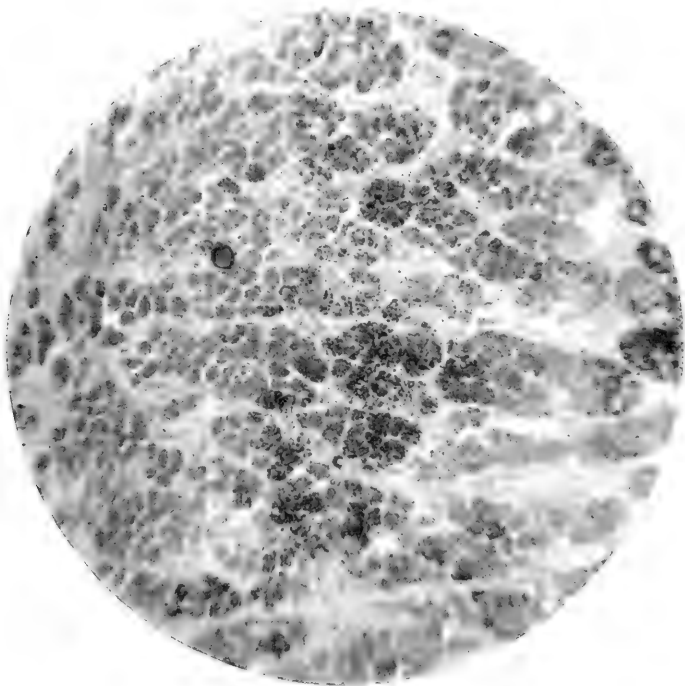


Fig. 9

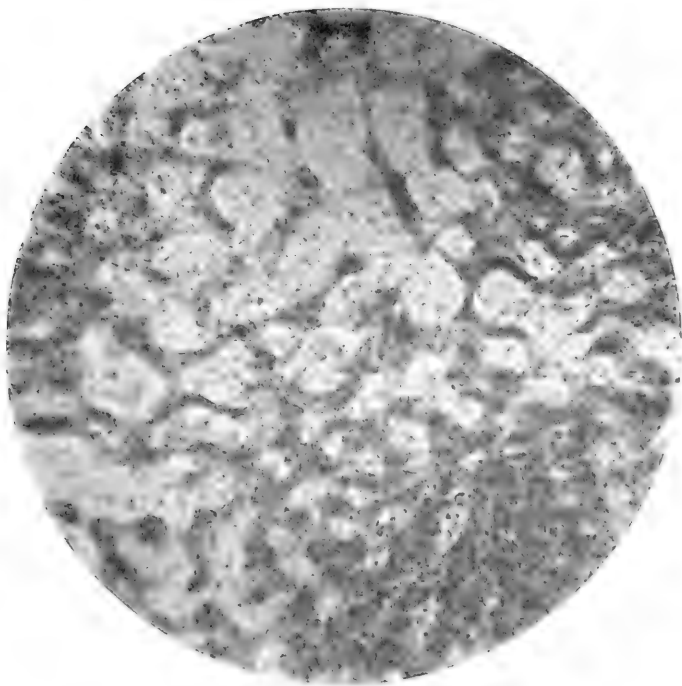


Fig. 10





*Fig. 11*



*Fig. 12*



# STUDIES IN THE TREATMENT OF MALARIA

## XIV. QUININE BIHYDROCHLORIDE GRAINS <sub>30</sub> INTRAMUSCULARLY, AND QUININE HYDROCHLORIDE GRAINS <sub>30</sub> ORALLY, DAILY, FOR <sub>12</sub> DAYS, IN SIMPLE TERTIAN MALARIA

BY

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This treatment (Aldershot, C 17) is recorded by Sir Ronald Ross in an 'Interim Report on the Treatment of Malaria,' issued by the War Office, 24/Gen. No. (A.M.D. 2) 6,198, presented 24th November, 1917, with Postscript, dated 4th March, 1918. The full description of the treatment is as follows:—

'Quinine bihydrochloride by intramuscular injection 15 grains simultaneously in each deltoid with 10 grains, orally, of hydrochloride thrice daily, totalling 60 grains daily, for 12 days. Patient remaining in bed for 12 days.

Given to 49 cases from 10th July, 1917, to 22nd October, 1917. Of these 5 relapsed (10 per cent.) up to the 31st December, 1917. Relapses occurred in an average of 34 days (extremes 16 to 72 days). Treatment quickly effective and well borne. Medical Officer thinks that the 12 days' rest in bed is of great value and would advocate 3 weeks of such rest. He thinks that this is the best form of treatment yet used by him. See remarks below.

*Remarks.*—On the 16th and 17th November, 1917, I inspected 79 of the men who had been through the Aldershot courses C 15, 16 and 17, and found that unfortunately many of them had been given daily doses of quinine (generally only 5 grains) by the Medical Officers of their units after they

had been discharged from the special malaria wards. The low proportion of relapses in these 3 treatments (8 to 20 per cent.) may be partly due to this continued medication; but as none of the 79 men had returned to hospital and only 6 of them looked at all unwell, I gathered that this continued medication had been unnecessary, and that most of the men had been really cured. Further study of these cases is in progress. See *Postscript*.\*

In the postscript dated 4th March, 1918, it is added:—

‘quinine was prohibited for all the 79 men examined by me in November, 1917, and every man was ordered to attend hospital weekly for clinical inspection, blood examination, and record of weight. Only 2 of these men have relapsed since then. On the 25th to 27th February, 1918, after my return from Salonika, I examined again 66 out of the 79 men, and concluded that they were all now probably free from infection. The figures for Treatments C 15 and 17 have been amended accordingly. With our present information, therefore, Treatment C 17 seems to be the best for resolving infections.’

Thirty cases were subjected to the treatment.\* A summary of the results of treatment is given in the Table, which also contains the following additional information:—Place of infection; and interval in months between present treatment and date of (*a*) first admission to a hospital for malaria, (*b*) leaving infected area, (*c*) arrival in England.

Blood examinations were made daily in all the cases.

Parasites disappeared from the blood, as a rule, in one to two days, in two cases in three days, and in two cases in four days. The temperature, as a rule, fell to normal either on the day of, or one day after, the commencement of treatment.

*Relapses.* In twenty-six of thirty cases a parasitic relapse occurred in eight to fifty-six days, average eighteen days. In four cases there was no parasitic relapse within an observation period of sixty-seven to a hundred days.

### CONCLUSION

The Aldershot C 17 Treatment, as described in an ‘Interim Report on the Treatment of Malaria’ issued by the War Office, may be followed by 87 per cent. of relapses within a post-treatment observation period of sixty days.

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\* The treatment administered was that described as C 17 in the Official Interim Report on the Treatment of Malaria 24/Gen No. (A.M.D.2) 6198 and circulated by the War Office at the beginning of April. This report was also read as a paper on Feb. 15th at the Society of Tropical Medicine and Hygiene. We find in *Trans. Soc. Trop. Med. & Hyg.* (issued June 1918) that at the adjourned discussion on this paper (March 15th) the treatment instead of lasting 12 days, is given as lasting 29 days. Our treatment is that described as C 17 in the Official Report.



TABLE  
Summary of results of Treatment C 17.

(Quinine bihydrochloride grains 30 intramuscularly and quinine hydrochloride grains 30 orally, daily for 12 days).

\* E.A. = East Africa. S. = Salonika.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of commencement of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Parasitic relapse occurred in — days after last dose	Febrile relapse (above 100° F.) occurred in — days after last dose	Observation period in cases in which did not relapse	Remarks
820	E.A.	10	3	2	4.5.18	Same day	2	12	16	...	
821	S.	8	5	3	24.4.18	1	2	13	16	...	
822	S.	6	2	1	7.5.18	1	2	13	16	...	
823	S.	18	2	1	25.4.18	1	1	16	14	...	
824	S.	9	2	1	25.4.18	Same day	1	...	...	67	
825	S.	23	2	1	24.4.18	1	2	10	14	...	100.2° on 1st day after end of treatment
826	S.	18	3	2	9.5.18	Same day	2	9	23	...	
827	S.	22	3	2	25.4.18	Same day	1	16	15	...	
828	S.	8	6	5	24.4.18	1	2	56	58	...	101° on last day of treatment; 100° on 1st day after, 102.2° on 2nd day after end of treatment. Quinine orally on 55th day
829	S.	10	2	2	9.5.18	1	2	53	...	...	
830	S.	15	2	1	14.5.18	Same day	1	13	16	...	
831	S.	20	4	3	9.5.18	1	2	12	16	...	
832	E.A.	13	2	1	25.4.18	1	1	21	21	...	
833	E.A.	13	3	1	26.4.18	1	2	19	22	...	
834	S.	14	4	3	9.5.18	1	2	11	14	...	100° on 4th day after end of treatment
835	E.A.	14	5	4	25.4.18	Same day	1	33	...	...	Parasites also found on 36th and 38th days. No febrile relapse in 57 days
836	E.A.	11	9	6	14.5.18	Same day	2	17	20	...	

## Summary of results of Treatment C 17.

(Quinine bihydrochloride grains 30 intramuscularly and quinine hydrochloride grains 30 orally, daily for 12 days).

\* E.A. = East Africa. S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of commencement of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Parasitic relapse occurred in — days after last dose	Febrile relapse (above 100° F.) occurred in — days after last dose	Observation period in days in cases which did not relapse	Remarks
837	S.	9	2	1	26.4.18	1	4	...	...	100	101° on 3rd day before end of treatment; 100° on 31st day after end of treatment
838	S.	14	4	3	7.5.18	1	2	15	17	...	Quinine orally on 13th day
839	E.A.	6	5	1	24.4.18	1	2	12	...	...	100° on 12th and 13th days after end of treatment
840	E.A.	9	6	5	25.4.18	1	2	19	18	...	101° and 100° on 6th and 14th days after commencement of treatment
841	S.	9	2	1	25.4.18	1	1	24	93	...	101° on 8th day; 102° on 9th day after commencement of treatment
842	S.	1	4	3	24.4.18	1	3	...	...	73	100° on 1st, 11th, 16th, 17th and 25th days after end of treatment
843	E.A.	6	4	2	7.5.18	1	2	21	25	...	102.2° on 3rd day; 102.4° on 14th day after commencement of treatment
844	S.	17	2	1	9.5.18	3	3	...	...	67	
845	S.	8	2	1	26.4.18	1	4	33	33	...	
846	E.A.	7	2	1	24.4.18	Same day	2	30	29	...	
847	S.	13	2	1	26.4.18	2	2	8	13	...	
848	E.A.	24	4	1	25.4.18	Same day	1	18	18	...	
849	S.	8	2	2	25.4.18	Same day	1	10	10	...	

# STUDIES IN THE TREATMENT OF MALARIA

## XV. A FACTOR HITHERTO OVERLOOKED IN THE ESTIMATION OF THE CURATIVE VALUE OF TREATMENTS OF MALARIA

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*Undertaken at the request of the War Office*

*(Received for publication 1 July, 1918)*

We consider it desirable to commence by re-stating the procedure to which we have strictly adhered throughout the whole of our work on the treatment of malaria, and by re-defining certain terms used by us in this paper which deals solely with simple tertian malaria.

- (a) No treatment was commenced before a microscopical diagnosis was made.
- (b) Blood examinations were with rare exceptions made daily after completion of treatment.
- (c) The relapses referred to in our work are without exception parasitic relapses. Febrile attacks unaccompanied by parasites in the blood within two to three days are not included, as the nature of these is unknown.
- (d) The term 'cure' is used by us throughout this paper to signify no parasitic relapse within an observation period of sixty days,\* after cessation of treatment: the observation period implying, as stated above, a *daily blood examination* after the cessation of treatment.

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\* This is, of course, purely an arbitrary period determined by the conditions under which we are working.

*Estimation of curative value of different treatments*

Consideration should convince anyone that for this purpose a post-treatment observation period is essential; blood examinations should be made as frequently as possible, for it is only by this means that malaria can be diagnosed with certainty. If the observation periods for all the cases in the different treatments are the same, then the results of these treatments are strictly comparable. If in certain treatments some of the cases are lost sight of before expiration of the maximum observation period, then in estimating the curative value of these treatments two figures must be given: (1) the number of relapses actually observed; this represents the minimum number of relapses. (2) the number of relapses actually observed plus the number of cases lost sight of before expiration of the full observation period; this represents the maximum number of relapses. For example, of the three treatments compared in Table I it is impossible to say whether Treatments I and II are better than III. It is fallacious to state that Treatment I is better than the others because only ten cases were known to relapse, as eighty cases were lost sight of, and may have relapsed, before completion of the full observation period of sixty days. Errors of this kind abound in the literature.

TABLE I.

Example of correct method of recording relapses.

Treatments	Number of cases treated	Number of cases which relapsed	Number of cases not relapsing but lost sight of before the expiration of 60 days	Number of cases not relapsing in an observation period of 60 days	Relapses
I.	100	10	80	10	10-90
II.	100	30	30	40	30-60
III.	100	50	0	50	50

We recorded (1918<sup>1</sup>) the results of treatment of seventy-six cases of simple tertian malaria by the administration of grains 90 of quinine sulphate in solution on each of two consecutive days only.

Subsequently (1918<sup>2</sup>) we recorded a second series of eighty-nine cases treated in the same way. Table II shews the number of cures obtained in each series.

TABLE II.

Treatment	Number of cases treated	Number of cases which relapsed	Number of cases not relapsing but lost sight of before the expiration of 60 days	Number of cases not relapsing in an observation period of 60 days	Cures	
					Max.	Min.
Series I ... ..	76	29	4	43	62 %	57 %
Series II ... ..	89	84	2	3	6 %	3 %

We propose to consider in this paper the factors which may explain the remarkable discrepancy between these results.

*Factor 1. The number of the cases*

What is the error that must be allowed for in comparing the results of observations based upon groups of seventy-six and eighty-nine cases respectively? Taking the error as approximately proportional to the square root of the number of cases observed, the corrected values would be for:—

Series I ... .. 46 to 68 per cent. of cures.

Series II ... .. 0 to 16 „ „

or by applying Poisson's formula\*:

Series I ... .. 41 to 73 per cent. of cures.

Series II ... .. 0 to 13 „ „

The figures do not overlap.

*Conclusion:* This factor cannot explain the discrepancy.

*Factor 2. The quinine solution and mode of administration*

The quinine solution was identical in both series, viz.: Howard's, and an analysis of the solutions used in the two series showed that the strength was correct. As regards mode of administration there was a slight difference in the two series, inasmuch as eighteen of the seventy-six cases of Series I had some portion of the (grains 180) dose of quinine given intramuscularly.

\* This formula for estimating liability to error is:  $\frac{m}{\mu} \pm 2\sqrt{\frac{2mn}{\mu^3}}$ . In this case  $m$  = percentage of cures,  $n$  = percentage of relapses,  $\mu$  = total cases.

If, however, we compare the fifty-eight cases of Series I with the eighty-nine of Series II, in which the mode of administration was entirely by the mouth, we get 63 per cent. of cures for the first series and 6 per cent. for the second.

*Conclusion:* This factor cannot explain the discrepancy.

*Factor 3. Strain of Parasite*

In Series I practically all the cases (seventy-two of seventy-six) were infected in Salonika. In Series II thirty-nine were infected in Salonika, forty-three in E. Africa.

TABLE III.

Factor 3: Strain of parasite.

Treatment	Salonika		E. Africa	
	Cases	Cures	Cases	Cures
Series I ... ..	72	65 %	...	...
Series II ... ..	39	3 %	43	7 %

Table III shows:—

(a) That in the second series of observations the percentage of cures is practically the same whether the cases were infected in Salonika or E. Africa.

(b) That amongst the Salonika cases 65 per cent. of the first series were cured, but only 3 per cent. of the second series.

*Conclusion:* This factor cannot explain the discrepancy.

*Factor 4. Length of time between date of infection and treatments under discussion*

The date of infection cannot be determined with exactitude, but we have been able to ascertain:—

A. The length of time between first reporting sick for malaria and the treatments.

TABLE IV.

Factor 4A : Length of time between first reporting sick and the treatments.

Treatment	0-12 months		13 months upwards	
	Cases	Cures	Cases	Cures
Series I ... ..	23	57 %	23	74 %
Series II ... ..	53	2 %	36	8 %

Table IV shows :—

(a) That in both the first and second series of observations there is not much difference in the percentage of cures whether the length of time since first reporting sick is under twelve months or over twelve months.

(b) That of the cases in which the length of time since first reporting sick is under twelve months the percentage of cures is much greater in Series I than in Series II; this applies also to the cases in which the length of time since first reporting sick is over twelve months.

B. Length of time between leaving the infected area and date of treatments.

TABLE V.

Factor 4B : Length of time between leaving infected area and date of treatments.

Treatment	0-9 months		10 months upwards	
	Cases	Cures	Cases	Cures
Series I ... ..	18	61 %	20	75 %
Series II ... ..	64	3 %	...	...

Table V shows :—

(a) That in the first series of observations there is not much difference in the percentage of cures obtained, whether the length of time since leaving the infected area is under nine months or over nine months.

(b) That among the cases which had left the infected area for a period of less than nine months the percentage of cures is much greater in Series I than in Series II.

*Conclusion:* This factor cannot explain the discrepancy.

*Factor 5. Length of time between arrival in England and treatments under discussion*

TABLE VI.

Factor 5: Length of time between date of arrival in England and the treatments.

Treatment	0-6 months		7 months upwards	
	Cases	Cures	Cases	Cures
Series I ... ..	24	71 %	17	65 %
Series II ... ..	64	5 %	...	...

Table VI shows:—

(a) That in the first series of observations there is not much difference in the percentage of cures whether the cases have been in England under six months or over six months.

(b) That of the cases which have been less than six months in England the percentage of cures obtained is much greater in Series I than in Series II.

*Conclusion:* This factor cannot explain the discrepancy.

*Factor 6. Time of year at which treatment was administered*

TABLE VII.

Factor 6: Time of year at which treatment was administered.

Treatment	Date	Cases	Cures	
			Maximum	Minimum
Series I ... ..	July-Sept., '17	76	62 %	57 %
Series II ... ..	Jan.-Apr., '18	89	6 %	3 %



TABLE VIII.

Shewing the Monthly (and Quarterly) percentage of Cures\* obtained from February, 1917 to April, 1918.

Nature and Duration of Treatment	1917												1918																							
	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Apr.	May																				
	R	†	C	R	C	R	C	R	C	R	C	R	C	R	C	R	C																			
Quinine bihydrochloride, grs. 15 intramuscularly on each of 2 consecutive days ...	5	0	14	1	...	...	...	...	...	...	...	...	...	...	...	...	...																			
Quinine bihydrochloride, grs. 10-15 intravenously (single injection)	1	0	5	0	...	...	...	...	...	...	...	...	...	...	...	...	...																			
Quinine bihydrochloride, grs. 10-15 intravenously thrice weekly for 2 weeks	6	0	6	1	...	...	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 15 orally on each of 2 consecutive days	...	...	2	0	12	0	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 10 orally on each of 2 consecutive days	...	...	10	0	...	...	...	...	...	...	...	...	...	...	...	...	...																			
Quinine bihydrochloride, grs. 5 orally on each of 2 consecutive days	...	...	10	0	8	0	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 30 orally on each of 2 consecutive days	...	...	...	...	14	0	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 45 orally on each of 2 consecutive days	...	...	...	...	9	3	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 30 orally daily for 8 weeks	...	...	...	...	24	5	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 30 orally daily for 3 weeks, and grs. 45 orally daily for 1 week	...	...	...	...	17	5	...	...	...	...	...	...	...	...	...	...	...																			
Quinine alkaloid, grs. 15-60 intramuscularly (either 1 or 2 injections)	...	...	...	...	12	3	19	4	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 30 orally daily for 5-18 weeks	...	...	...	...	6	0	3	1	1	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 5 orally on each of 2 consecutive days...	...	...	...	...	11	1	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 60 orally on each of 2 consecutive days	...	...	...	...	7	5	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 20 orally daily for 14-15 weeks	...	...	...	...	3	2	...	...	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 45 orally daily for 3-8 weeks	...	...	...	...	7	10	0	2	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 45 orally on 2 consecutive days weekly for 8 weeks	...	...	...	...	5	8	1	7	...	...	...	...	...	...	...	...	...																			
Quinine sulphate, grs. 90 orally on each of 2 consecutive days (1st series)	...	...	...	...	...	10	8	11	23	8	16	...	...	...	...	...	...																			
Quinine sulphate, grs. 10 orally on 2 consecutive days weekly for 8-16 weeks	...	...	...	...	...	5	9	1	1	1	0	...	...	...	...	...	...																			
Quinine sulphate, grs. 90 orally on 2 consecutive days weekly for 3 weeks	...	...	...	...	...	0	1	0	2	1	2	9	5	1	2	0	1																			
Quinine sulphate, grs. 120 orally on each of 2 consecutive days	...	...	...	...	...	...	...	...	4	3	5	3	...	...	...	...	...																			
Novarsenobillon, gm. 0.4, single intravenous injection	...	...	...	...	...	...	...	...	...	5	1	4	1	...	...	...	...																			
Quinine sulphate, grs. 90 orally on each of 2 consecutive days (2nd series)	...	...	...	...	...	...	...	...	...	...	...	2	0	8	0	41	2																			
Novarsenobillon, gm. 0.6, single intravenous injection	...	...	...	...	...	...	...	...	...	...	...	...	5	0	16	1	...																			
Novarsenobillon, gm. 0.9, single intravenous injection	...	...	...	...	...	...	...	...	...	...	...	...	...	...	9	0	8																			
217. Quinine bihydrochloride, grs. 30 intramuscularly, and quinine hydrochloride, grs. 30 orally daily for 12 days	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	25	5																			
Totals	12	0	27	2	32	0	90	16	55	33	17	28	12	26	14	21	14	8	6	3	4	2	5	0	16	0	57	3	41	4	33	8				
Percentage of cures each month ...	0	7	0	15	5	37	0	36	0	33	0	33	0	36	0	33	0	36	0	33	0	33	0	0	16	0	57	3	41	4	33	8				
Percentage of cures each quarter	5	7	0	21	7	0	63	0	35	0	33	0	63	0	35	0	35	0	35	0	33	0	33	0	0	16	0	57	3	41	4	33	8			
	21.7%												35.2%												3.7%											

\* By 'Cure' is meant no parasitic relapse within a post-treatment observation period of 60 days.

† R = Relapses.

C = Cures.

Table VII shows that whilst the first series of cases were treated in July, August and September, 1917, the second series were treated in January, February, March and April, 1918.

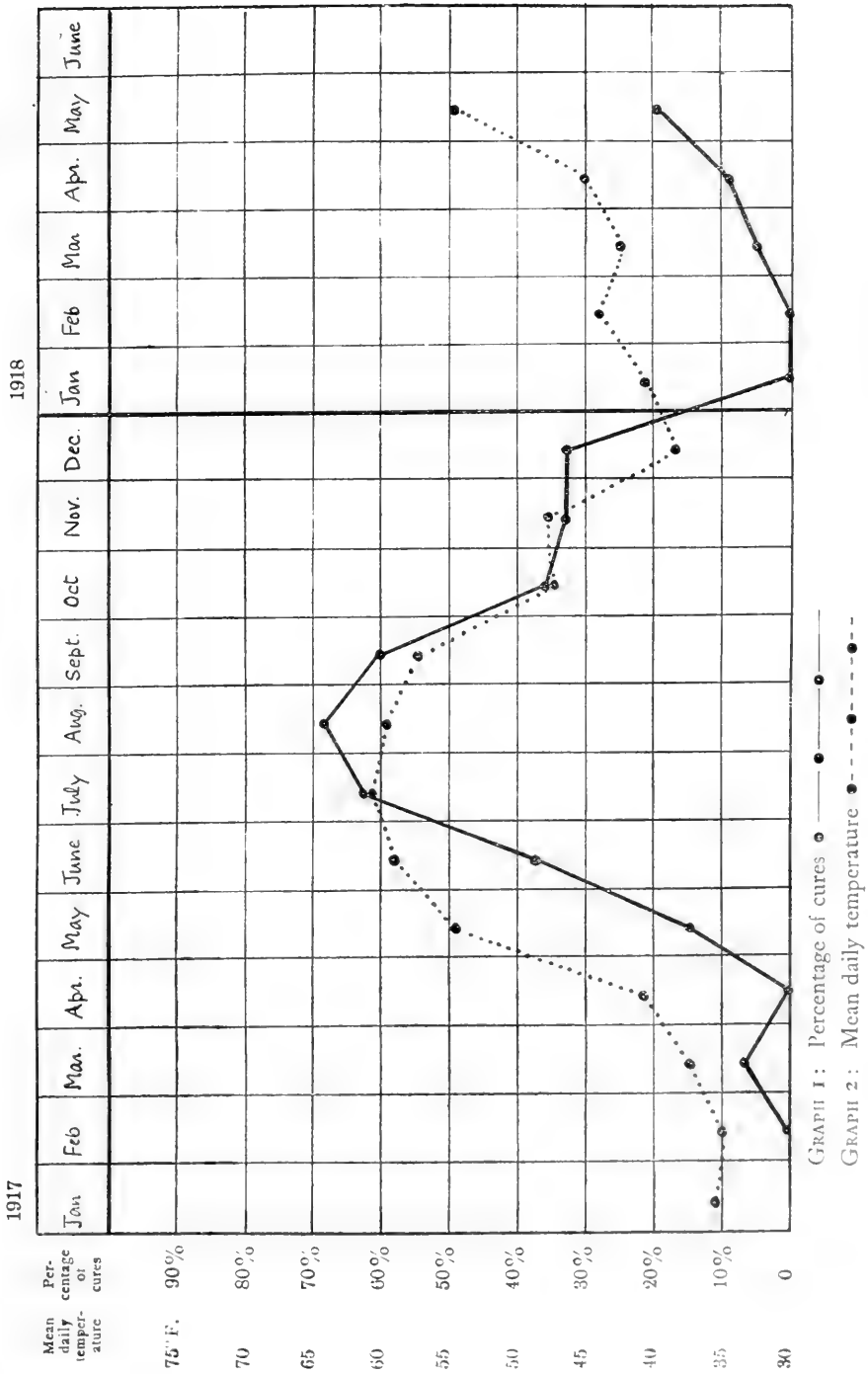
*Conclusion:* This factor may possibly explain the discrepancy.

We proceeded, therefore, to enquire whether the data in our possession supported this explanation. In Table VIII we have arranged all the cases treated by us during the last seventeen months, irrespective of the nature of the treatment to which they were submitted, according to the month in which the treatment ended. In each vertical column the number of relapses and of cures among the cases completing treatment in each month are given, and at the foot of each column is the monthly percentage of cures obtained; in addition the percentages of cures for each quarter of the year are recorded. The data are also shown in Graph 1.

It will be seen that Graph 1, which represents the percentage of cures obtained, varies with the month of the year in which the treatment ended; broadly speaking, a very small percentage of cures is obtained in the winter and spring and a comparatively high percentage in the summer and autumn. These facts, then, support the hypothesis that the discrepancy between the results obtained in the first and second series of treatments, by quinine grains 90 on each of two consecutive days, is due to the different periods of the year at which the treatments were administered.

With a view to examining this question more fully, we have obtained the meteorological observations made at the Liverpool Observatory from January, 1917, to May, 1918, and so far as we can see, the only meteorological factors that are in any way correlated with the seasonal variation in the percentage of cures obtained by us are the variations in the mean temperature, and prevalence of the east wind. The average mean daily temperature for each month during the period January, 1917, to May, 1918, is given in Graph 2. It will be seen that the general form of this agrees with that of Graph 1 representing the monthly percentage of cures effected by our treatments. The higher the mean daily temperature the higher the percentage of cures.

These observations apply to England. We are unable to say whether or not they have any application to other countries where the seasons are different or to climates in which the



meteorological conditions are not comparable. Our data are also at present insufficient to show whether the more favourable results obtained by treatments carried out during the summer were due to the occurrence of actual cures, or only to a prolongation of the period of latency. We are also at present unable to say if treatments with smaller doses of quinine than grains 90 on two consecutive days would or would not be equally effective if administered during the summer months.

Whether or no we are correct in our conclusion that the season at which treatment for malaria is given influences the results obtained, there seems to be no doubt that we must recognise the fact that the same treatment if carried out on different occasions may give quite dissimilar results.

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# STUDIES IN THE TREATMENT OF MALARIA

## XVI. INTRAVENOUS INJECTIONS OF NOVARSENOBILLON IN SIMPLE TERTIAN MALARIA

BY

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In each of the following series a single injection only of novarsenobillon was given. The results are summarized in the tables, which also contain the following additional information:—Place of infection, and interval in months between present treatment and (a) first admission to a hospital for malaria, (b) leaving infected area, (c) arrival in England.

### 0.45 GRAMME SERIES (Cases 850-869)

A single injection of 0.45 gramme of novarsenobillon\* was given in twenty cases. Blood examinations were made daily in all the cases. Parasites disappeared from the blood in one to two

\*Novarsenobillon (Novarsenobenzol Billon) is the dioxydiaminoarsenobenzene mono-methylene sulphonylate of soda, the salt described by Ehrlich under the title of '914.'

days. The temperature fell to normal either on the day of the injection or in one to three days.

*Relapses.* In seventeen of the twenty cases a parasitic relapse occurred in eleven to twenty-seven days, average eighteen days. In three cases (853\*, 858 and 869) there was no relapse within an observation period of sixty days. In the seventeen cases which relapsed parasitically, febrile relapses occurred in fifteen to thirty days, average twenty days. In one case (858) which did not relapse parasitically there were numerous non-parasitic febrile attacks after treatment.

#### 0.6 GRAMME SERIES (Cases 870-892)

A single injection of 0.6 gramme of novarsenobillon was given in twenty-three cases. Blood examinations were made daily in all the cases. Parasites disappeared from the blood in one to two days. The temperature fell to normal either on the day of the injection or in one to two days.

*Relapses.* In twenty-two of the twenty-three cases a parasitic relapse occurred in ten to forty-six days, average twenty days. In the remaining case (884), there was no relapse within an observation period of one hundred and eight days. In twenty-one of the twenty-two cases, which relapsed parasitically, febrile relapses occurred in fourteen to fifty-seven days, average twenty-four days. In the remaining case (883) quinine was given on the twenty-fifth day. In one case (884) which did not relapse parasitically there was a low irregular temperature throughout; a diagnosis of liver abscess was made on the physical signs, but no pus was found at operation.

#### 0.9 GRAMME SERIES (Cases 893-913)

A single injection of 0.9 gramme of novarsenobillon was given in twenty-one cases. Blood examinations were made daily in all the cases. Parasites disappeared from the blood in one day in twenty cases, in two days in the remaining case. The temperature fell to normal either on the day of the injection or in one to two days.

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\* This case relapsed in 105 days.

TABLE I

Summary of results of a single intravenous injection of novarsenobillon grm. 0.45, in simple tertian malaria.

\* E.A. = East Africa. S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after injection	Parasites disappeared from cutaneous blood in — days after injection	Parasitic relapse occurred in — days after injection	Febrile relapse (above 100° F.) occurred in — days after injection	Observation period in days in cases which did not relapse	Remarks
850	...	...	...	...	13.11.17	1	2	16	20	...	
851	...	...	...	...	16.11.17	1	2	28	29	...	
852	...	...	...	...	16.11.17	1	2	12	15	...	
853	...	...	...	...	19.11.17	1	1	...	...	90*	99° F. on 50th; 103° F. on 56th; 99° F. on 89th days
854	...	...	...	...	19.11.17	3	2	13	15	...	
855	...	...	...	...	26.11.17	1	2	25	24	...	
856	...	...	...	...	17.12.17	1	1	20	23	...	
857	...	...	...	...	17.12.17	Same day	1	18	21	...	
858	E.A.	12	10	5	19.12.17	Same day	1	...	...	67	
859	...	...	...	...	19.12.17	1	2	23	25	...	
860	...	...	...	...	19.12.17	Same day	1	27	30	...	
861	...	...	...	...	4.1.18	Same day	2	18	19	...	
862	E.A.	6	...	...	7.1.18	Same day	2	15	16	...	
863	...	...	...	...	17.1.18	1	1	22	23	...	
864	S.	14	...	...	4.2.18	1	1	18	18	...	
865	S.	7	...	...	4.2.18	Same day	1	11	15	...	
866	...	...	...	...	4.2.18	Same day	1	14	16	...	
867	S	18	3	3	27.4.18	1	1	13	13	...	
868	S.	10	3	2	2.5.18	Same day	1	16	16	...	
869	...	...	...	...	3.5.18	Same day	1	...	...	60	

\*This case relapsed parasitically in 105 days.

TABLE II.

Summary of results of a single intravenous injection of novarsenobillon grm. 0.6, in simple tertian malaria.

\* E.A. = East Africa. F. = France. S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after injection	Parasites disappeared from cutaneous blood in — days after injection	Parasitic relapse occurred in — days after injection	Febrile relapse (above 100° F.) occurred in — days after injection	Observation period in days in cases which did not relapse	Remarks
870	F.	6	...	...	11.2.18	Same day	1	27	29	...	
871	E.A.	17	...	...	15.2.18	Same day	1	21	21	...	
872	S.	22	2	1	15.2.18	Apyrexia	2	46	50	...	
873	S.	16	...	...	25.2.18	2	2	16	18	...	
874	E.A.	12	3	2	25.2.18	Same day	1	34	57	...	100° F. on 6th and 8th days after injection. Gamete on 34th day; trophozoite on 35th day; then negative till 56th day.
875	...	...	...	...	2.3.18	Same day	1	24	24	...	
876	...	...	...	...	2.3.18	1	2	14	17	...	
877	...	...	...	...	5.3.18	1	2	23	24	...	
878	S.	21	3	2	6.3.18	1	1	19	19	...	
879	...	...	...	...	14.3.18	Same day	1	15	17	...	
880	S.	18	...	...	14.3.18	1	1	17	22	...	
881	S.	18	2	1	16.3.18	2	2	12	14	...	
882	...	...	...	...	16.3.18	Same day	1	10	15	...	
883	...	...	...	...	25.3.18	1	1	25	...	...	Quinine orally on 25th day.
884	...	...	...	...	25.3.18	...	1	...	...	108	Low irregular temperature throughout.
885	S.	20	2	1	25.3.18	Same day	2	16	23	...	
886	S.	9	1	1	27.3.18	1	1	15	18	...	
887	S.	9	...	...	27.3.18	Same day	1	13	18	...	
888	S.	18	2	1	28.3.18	Same day	1	16	18	...	
889	S.	16	...	...	28.3.18	Same day	2	13	17	...	
890	S.	21	2	1	28.3.18	Same day	1	18	20	...	
891	S.	19	...	...	28.3.18	Apyrexia	1	19	23	...	
892	S.	10	3	2	18.5.18	Same day	2	40	40	...	



TABLE III.

Summary of results of a single intravenous injection of novarsenobillon grm. 0.9 in simple tertian malaria.

\* E.A. = East Africa. It. = Italy. S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after injection	Parasites disappeared from cutaneous blood in — days after injection	Parasitic relapse occurred in — days after injection	Febrile relapse (above 100° F.) occurred in — days after injection	Observation period in days in cases which did not relapse	Remarks
893	S.	19	3	2	27.4.18	Same day	1	15	15	...	
894	It.	8	1	1	28.4.18	1	1	17	17	...	
895	S.	19	3	2	28.4.18	1	1	17	18	...	
896	S.	6	3	2	28.4.18	2	1	17	18	...	
897	E.A.	8	2	1	30.4.18	Same day	1	21	24	...	
898	S.	8	2	1	30.4.18	Same day	1	15	18	...	
899	S.	8	4	1	30.4.18	Same day	1	14	15	...	
900	S.	8	3	2	30.4.18	Same day	1	21	23	...	
901	S.	7	2	2	30.4.18	1	1	21	22	...	
902	S.	12	4	3	1.5.18	1	1	...	...	37	Quinine orally on 37th day.
903	E.A.	7	5	2	1.5.18	1	1	19	21	...	
904	S.	26	3	3	1.5.18	Same day	2	17	20	...	
905	S.	13	3	2	1.5.18	1	1	...	...	60*	
906	S.	9	4	3	2.5.18	1	1	16	19	...	
907	S.	21	3	2	2.5.18	Apyrexia	1	14	19	...	
908	S.	8	2	2	2.5.18	Same day	1	16	17	...	
909	E.A.	10	4	2	2.5.18	Same day	1	47	48	...	
910	S.	9	5	2	3.5.18	1	1	15	16	...	
911	S.	12	3	2	3.5.18	Apyrexia	1	31	30	...	
912	S.	14	3	2	3.5.18	Same day	1	5	14	...	Gametes very scanty on 5th day; trophozoites on 16th day.
913	S.	8	7	6	18.5.18	1	1	24	26	...	

\* This case relapsed parasitically in 63 days.

*Relapses.* In nineteen of the twenty-one cases a parasitic relapse occurred in five to forty-seven days, average nineteen days. In one case (902) there was no relapse within an observation period of thirty-seven days, when quinine was administered by mistake. In the remaining case (905\*) there was no relapse within an observation period of sixty days. In eighteen of the nineteen cases which relapsed parasitically, febrile relapses occurred in fourteen to forty-eight days, average twenty-one days.

### CONCLUSION

Single intravenous injections of novarsenobillon in doses varying from 0.45 to 0.9 gramme control the febrile paroxysms and cause the disappearance of parasites from the cutaneous blood, as a rule within one day, in simple tertian malaria. Parasitic relapses occur, on an average, in twenty-one days. The curative effect of a single injection of the drug in the doses used is practically nil.

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\* This case relapsed in 63 days.

# STUDIES IN THE TREATMENT OF MALARIA

## XVII. ORAL ADMINISTRATION OF QUINO- TOXIN FOR TWO CONSECUTIVE DAYS ONLY IN SIMPLE TERTIAN MALARIA

BY

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*Undertaken at the request of the War Office*

*(Received for publication 31 July, 1918)*

At the suggestion of Professor Ramsden we decided to test the action of quinotoxin\* on the parasites and the fever in cases of simple tertian malaria.

A solution of quinotoxin hydrochloride was prepared for us by Professor Ramsden.

A dose corresponding to grains 5 of this salt was given orally to five patients (914-918), and grains 10 to four patients (919-922), on each of two consecutive days.

Blood examinations were made daily in all cases.

In the temperature charts :—

Q.T. = oral administration of solution of quinotoxin.

gr. = grains of hydrochloride of quinotoxin.

T. = simple tertian trophozoites or schizonts.

G. = simple tertian gametes.

Neg. = no parasites found.

\* = oral administration of solution of quinine sulphate.

\* Professor Ramsden deals with the pharmacology of quinotoxin in a subsequent paper (these *Annals*, p. 233).

The results are summarised in the Table, where the following information is also given:—Place of infection, and interval in months between present treatment and (a) first admission to a hospital for malaria; (b) leaving infected area; (c) arrival in England.

Quinotoxin, in the doses used, failed to control the temperature or cause the disappearance from the peripheral blood of parasites in cases of simple tertian malaria (*vide* charts).

In a previous paper (1918), we have on the contrary shewn that grains 5 of quinine sulphate on each of two consecutive days only, caused the disappearance of parasites in eight of twelve cases, and brought the temperature to normal within a few days in ten of twelve cases; also that grains 10 of quinine sulphate on each of two consecutive days caused the disappearance of the parasites and fall of the temperature to normal in all of ten cases.

TABLE

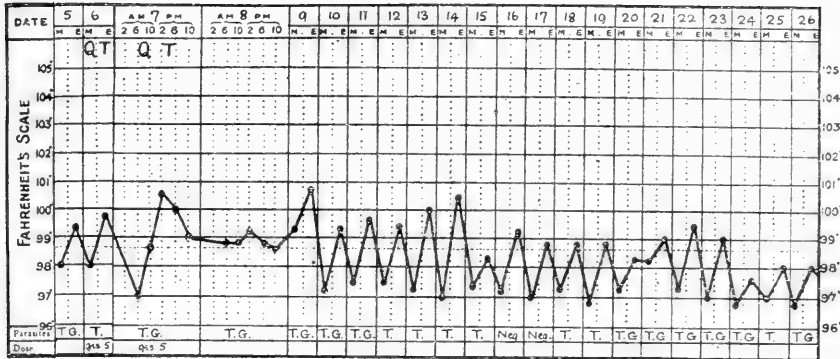
Summary of results of administration of quinotoxin in simple tertian malaria.

• S = Salonika. E.A. = East Africa.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and date of present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Result of treatment
914	S.*	9	4	4	7.6.18	Parasites persist; temperature uncontrolled.
915	E.A.	9	4	3	8.6.18	Parasites persist; temperature fell to normal in two days.
916	S.	21	6	1	12.6.18	Parasites persist; temperature uncontrolled.
917	S.	19	5	4	12.6.18	Parasites persist; temperature uncontrolled.
918	S.	9	2	1	12.6.18	Parasites persist; temperature uncontrolled.
919	S.	23	2	1	14.6.18	Parasites persist; temperature fell to normal in two days.
920	S.	4	1	0	25.6.18	Parasites persist; temperature uncontrolled.
921	S.	11	1	0	25.6.18	Parasites persist; temperature uncontrolled.
922	S.	7	2	1	26.6.18	Parasites persist; temperature uncontrolled.

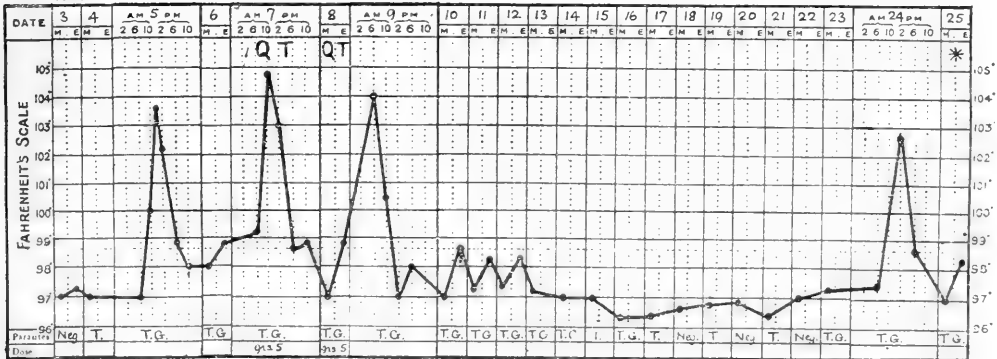
## CASE 914

June



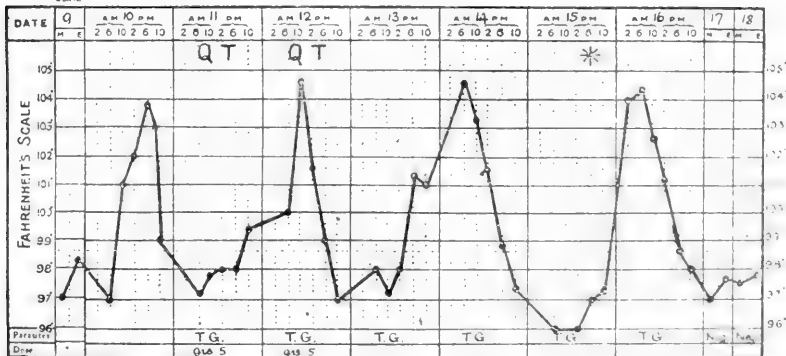
## CASE 915

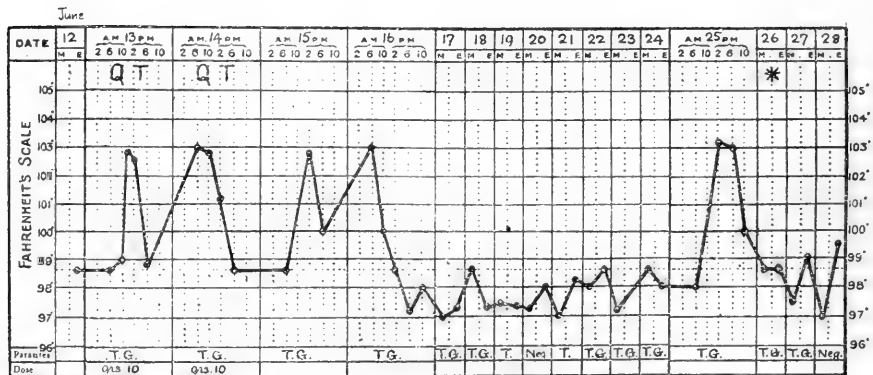
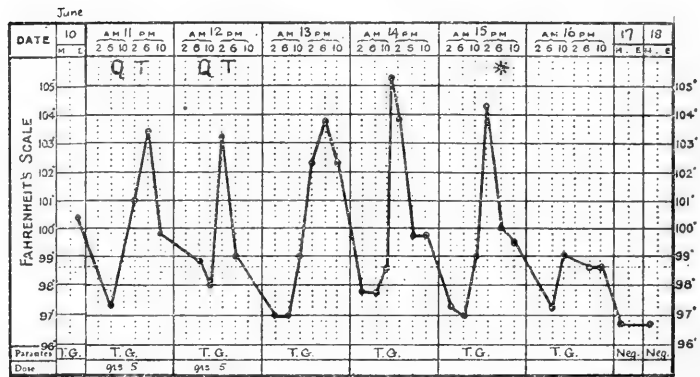
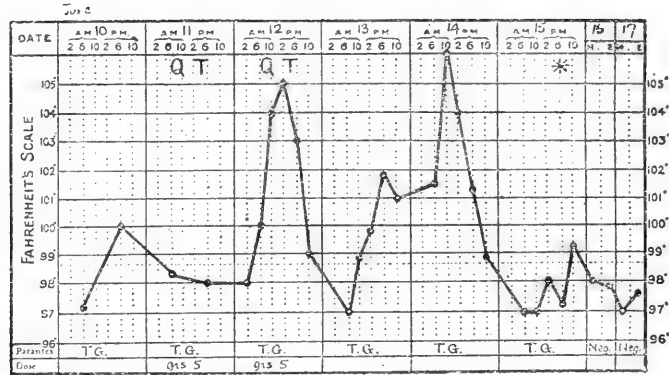
June



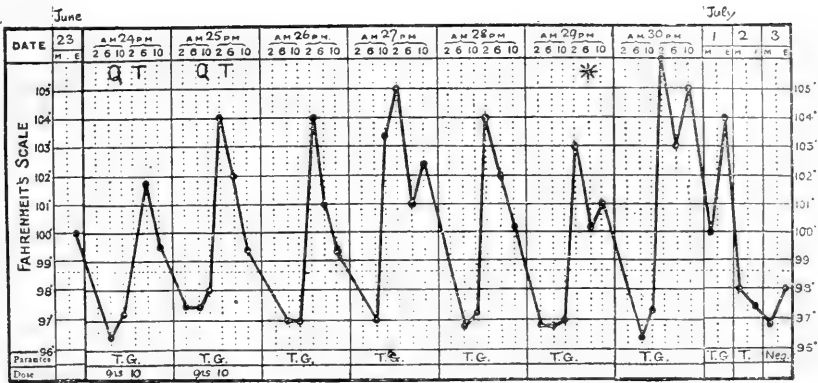
## CASE 916

June

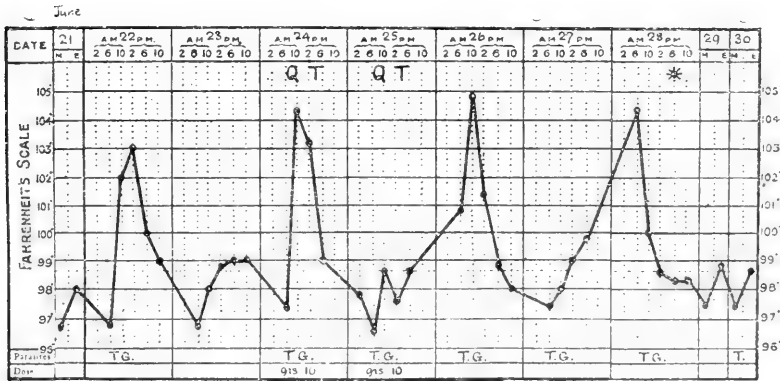




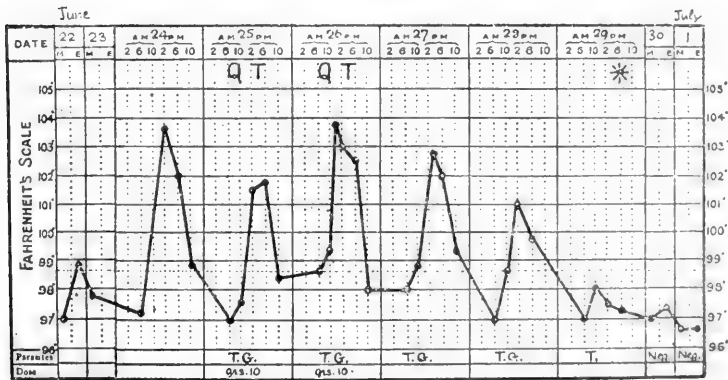
## CASE 920



## CASE 921



## CASE 922



### CONCLUSION

Quinotoxin hydrochloride in the doses used, grains 5 and grains 10 on each of two consecutive days, has practically no action on the parasites or the fever, and so is inferior in its action to similar doses of quinine sulphate in simple tertian malaria.

### REFERENCE

- STEPHENS, J. W. W., YORKE, W., BLACKLOCK, B., MACFIE, J. W. S., COOPER, C. F., and CARTER, H. F. (1918). *Ann. Trop. Med. & Parasitol.*, Vol. XI, pp. 284 and 289.



# ON QUININE IN ANIMAL TISSUES AND LIQUIDS, WITH METHODS FOR ITS ESTIMATION

BY

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*From the Department of Bio-Chemistry, University of Liverpool*

*Report to the Medical Research Committee*

*(Received for publication 12 August, 1918)*

## INTRODUCTION

Our main objects in the work recorded below have been :—

1. To devise methods delicate enough for the estimation of quinine in the various organs, tissues and liquids of the animal body.
2. To apply these methods and obtain information concerning the quinine-content of the blood, urine, and tissues, and the metabolism of quinine in the body in the hope that light would thereby be thrown on the problems of blackwater fever, quinine intoxication, and the therapeutics of malaria.

Many previous observers have investigated the elimination of quinine in urine and faeces, and the more important results of their labours may be briefly stated as :—

- (i) proof that of the quinine administered, whether by mouth or by intravenous or intramuscular injection, only a fraction, varying with different patients from 23 to 66 per cent., reappears in the urine;

(ii) proof that, except when given in some insoluble form such as the tannate, any elimination of quinine by the faeces is ordinarily so slight as to be negligible;

(iii) evidence that no recognizable derivative of quinine is excreted in the urine;

(iv) evidence that quinine administered in solution by the mouth is absorbed with great rapidity, and appears in the urine almost as rapidly as when it is administered intravenously.

For an adequate understanding of the methods described below, reference to a paper recently published by two of us (8) describing a method for the extraction and nephelometric estimation of the minute amounts of quinine occurring clinically in human blood and urine is essential.

#### **METHOD OF ESTIMATION APPLICABLE TO MOST TISSUES (AMMONIUM SULPHATE METHOD)**

About 5 grams of the tissue is transferred direct from the animal into a weighed flask containing about 10 c.c. of a saturated aqueous solution of ammonium sulphate and 0.6 per cent. sulphuric acid. The flask is re-weighed, then boiled for two minutes and its contents filtered under pressure through a Gooch crucible or Buchner filter. The residue is then pulped in a mortar with glass-powder and again boiled up in the original flask with successive lots of acidulated ammonium sulphate solution. The combined filtrates are shaken with ether to extract oily matters, then alkalisied strongly with ammonia and again shaken up with ether to extract the quinine. The quinine obtained is estimated nephelometrically exactly as in the method for blood.

The method has been laboriously tested with each of the tissues referred to in the following table. The tissues were first reduced to a pulp. About 5 grams of the pulp were then mixed thoroughly with a measured volume of a solution of quinine hydrochloride. In many cases the mixture stood half an hour or more before it was boiled with acidulated ammonium sulphate solution. The observers did not know the correct results beforehand.

## CONTROL ESTIMATIONS WITH THE AMMONIUM SULPHATE METHOD.

Tissue	Animal	Mgms. Q. Added	Found	Error %
Spleen	Guinea-pig	0.05	0.049	- 2.5
"	"	0.04	0.0385	- 4
Kidney	"	0.048	0.045	- 4.8
"	"	0.05	0.048	- 5
Suprarenal	"	0.05	0.048	- 5
"	"	0.04	0.0385	- 4
Muscle	"	0.05	0.0476	- 4.8
Liver	"	0.05	0.04	- 20
"	"	0.05	0.0384	- 23
"	"	0.05	0.0435	- 13
Brain	Sheep	0.10	0.05	- 50
"	"	0.05	0.35	- 30
"	"	0.10	0.05	- 50

Qualitative control experiments have been made in each case and also with bone-marrow and beef-suet. In the absence of quinine, an absolutely negative Tanret turbidity test was found invariably.

The results have been, as shown by the table, invariably deficits. With none of the tissues examined, however, except liver and brain, have these deficits exceeded 5 per cent. of the minute total, and we believe them to have been due within this limit largely to losses in manipulation of the ether used for extracting the quinine.

It is probable that a simple method which is capable of giving results like the above in an average time of one and a half hours, or some slight modification of it adapted for the particular alkaloid sought, would be found very useful in medico-legal and pharmacological work.

With brain and liver, the deficits ranged from 13 per cent. to 50 per cent., and it appeared at first probable either that boiling the tissues with saturated  $\text{Am}_2\text{SO}_4$  solution failed to extract the whole of the alkaloid, or that some other substance which diminished the Tanret turbidity was extracted with it.

Various alcohol-extraction methods were accordingly devised, and after many failures, the following procedure was found to give accurate results in the case of brain and fat, but in the case of liver deficits even greater than those found by the first process. We have not tested it with faeces.

#### ALCOHOL EXTRACTION METHOD

Weigh out about 10 grams of tissue, grind up to a fine pulp with powdered glass and transfer it to a flask, with the aid of boiling absolute alcohol. Boil and filter into a graduated cylinder. Repeat the boiling and filtering with three further lots of alcohol. Note the volume of filtrate, pour it into five times its volume of 1 per cent. sulphuric acid and shake thoroughly for five minutes. Extract its fats by shaking with three successive lots of pure ether. For every 100 c.c. of the fat-free liquid add 5 c.c. of 25 per cent. lead acetate solution and filter off an aliquot portion of the whole into a stoppered cylinder. Saturate it with ammonium sulphate, pipette off the layer of alcohol-ether which separates, and again extract with ether until the extracts are colourless. Alkalise with ammonia and extract the quinine with four successive lots of ether, evaporating each lot as it separates in one of the tubes gauged for nephelometry. Dissolve the residual quinine by boiling it with a sufficiency of a known volume of saturated aqueous ammonium sulphate, and estimate it nephelometrically.

#### CONTROL ESTIMATES BY THE ALCOHOL-EXTRACTION METHOD.

Tissue	Animal	Mgms. Q. added	Found	Error %
Brain	Sheep	0.10	0.095	- 5
"	"	0.025	0.0254	+ 1.6
"	"	0.05	0.048	- 4
Liver	Guinea-pig	0.10	0.066	- 33
"	"	0.05	0.0385	- 23
Liver	Ox	0.10	0.03	- 66
"	"	0.10	0.04	- 60
"	"	0.059	0.0286	- 51

It was evident from the good results with brain that the large deficits found by the alcohol method when applied to liver were not due to incomplete extraction of quinine.

Trying the ammonium sulphate method again, but with the variation that the liver pulp was boiled *before* the quinine was added, it was found to give results as accurate as those obtained with spleen, kidney, suprarenal, etc. This finding made the idea of an interfering substance in liver which diminished Tanret turbidity a very improbable one, and forced us to contemplate the possibility that the liver rapidly destroyed quinine or in some way modified it even post-mortem.

The experiments recorded on pp. 230-233 below show the interesting fact that this is actually the case, and also that the quinine is altered under conditions which preclude general protoplasmic activity. They show further that this rapid alteration is the sole cause of the large deficits obtained by the ammonium sulphate process when applied to liver, and that when the liver pulp was 'inactivated' at once after adding the quinine by saturating it with ammonium sulphate the method gave excellent results, results, *vide* p. 232, Exp. E.

Pending definite knowledge whether other tissues\* differ from liver only in the rapidity of their action on quinine or whether they are entirely inactive, the precaution of boiling all the tissues as soon as possible is clearly advisable.

#### DETECTION OF QUININE IN FAECES

Grind about 10 grams of faeces with enough 1 per cent. sulphuric acid to make a fine suspension, acid in reaction, and transfer it to a beaker. Add ammonium sulphate till saturated, boil for a few minutes and filter under suction through a Buchner funnel. For every 10 c.c. of filtrate add 0.5 c.c. of 25 per cent. lead acetate solution—and filter—the precipitated lead salts carry down with them some substance which would otherwise appear in the final product and give Tanret turbidity. Shake up the acid filtrate with three successive 8 c.c. lots of purified ether to remove 'oily matters'; then alkalisise with ammonia and shake up with three further lots of ether to extract the quinine. To the residue left when the ether is

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\* We have recently ascertained that guinea-pig's muscle destroys quinine under similar conditions.

evaporated off, apply either the Herapathite or the Tanret turbidity test. The above procedure easily detects 0.01 mgm. of quinine in 10 grams of faeces. It does not, however, give correct quantitative results by the nephelometric method—the amounts found are usually about 60 per cent. of the amount added, and must therefore be regarded as minimal.

#### RESISTANCE OF QUININE TO CHANGE IN PUTRIFYING FAECES AND URINE

We have not ascertained the cause of the deficit found in the nephelometric estimate of quinine in faeces. If we may judge by a single experiment, it is not due to destruction of quinine by faecal bacteria. To 100 c.c. of a thin cream of faeces rubbed up with water, 5 mgms. of quinine were added in feebly acid solution. Immediate estimation gave 3.1 mgms. Estimation after three days' incubation at 37°C. gave 3.15 mgms. Typical Herapathite crystals were obtained.

Similarly with 250 c.c. of putrifying urine to which 0.625 mgm. of quinine were added. Samples, each of 50 c.c., were taken at intervals. The reaction remained acid throughout. Estimated at once, 97 per cent. was found; after 2, 8, and 31 days respectively, 98 per cent., 96 per cent. and 98 per cent. were found.

In another urine after eight days alkaline putrifaction at laboratory temperature the amount found was exactly equal to that originally added.

#### ESTIMATE OF QUININE IN BILE

The bile is first of all 'defaecated' precisely as if it were so much urine (8). An aliquot part of the filtrate is then treated by the ammonium sulphate method described for blood and the extracted quinine is estimated nephelometrically.

	Mgms. of quinine given	Mgm. found	Error %
Ox bile (5 c.c.)	0.04	0.03846	- 4.0
„ „	0.20	0.1925	- 4.0

## DETECTION OF QUININE IN SPUTUM, GASTRIC CONTENTS OR MILK

Treat exactly as if so much blood. Control experiments have shown that in the absence of quinine the residue finally obtained gives not a trace of Tanret turbidity. We have not made quantitative estimations, but have little doubt that the method would give good results.

### ADDENDA ON THE ESTIMATION OF QUININE IN BLOOD

We have had extensive experience of the nephelometric method recently published by two of us, and the following additional instructions and comments should be found useful:—

1. Great care must be taken to dissolve in the saturated  $\text{Am}_2\text{SO}_4$  solution every trace of the extracted quinine. To do so without risk of altering the quinine by excessive heat, it is well to heat the test-tube and its contents in a brine bath.

2. Differences of as little as 2 per cent. in the quinine-content of two solutions can be detected with certainty by means of the adjustable-slit nephelometer devised by one of us (W. R.) provided the matching tubes are of exactly equal calibre and the observer is not fatigued. We find it best to make the whole series of matching tubes ourselves out of a single piece of 'quill' glass tubing, 13 mm. in diameter, along which a closely-fitting cork can be moved with equal friction throughout its entire length.

3. We find it advantageous to place all the matching tubes with their turbid contents in a bath of boiling brine or saturated ammonium sulphate for a few minutes until they become clear. Then cool equally in running water for ten minutes. Perfect mixing is secured, the turbidity reappears unimpaired, and any effects due to original differences in the time and rate of mixing with Tanret's reagent are completely eliminated. This treatment cannot be repeated more than once without risk of introducing error.

4. When the total quinine is not more than 0.01 mgm., 2 c.c. of saturated sulphate solution (instead of 5 c.c.) should be used to dissolve it, and a correspondingly reduced volume of Tanret's reagent added. In 13 mm. test-tubes the height of the column amply suffices for the nephelometer, and the greater concentration of the quinine permits 0.005 mgm. to be estimated.

5. We have ascertained for the benefit of workers in hot climates that for the estimation of quinine in blood medicinal chloroform may, without any loss of accuracy, be substituted for the ether. This is not true for urine.

### ACTION OF LIVER ON QUININE

The selected experiments recorded below supply further detail concerning the conversion of quinine effected by the liver. The rate of change is at first rapid, but soon slows down. When it is complete, the residue of an ether extract of the alkalisied liver preparation gives not a trace of Tanret turbidity; the product is therefore presumably not alkaloidal, and is certainly not quinotoxin. What it is our experiments do not show. They have been directed to ascertain first of all what conditions as regards antiseptics, reaction, and oxygen supply are favourable, and how the active agent or agents can be obtained free from gross accompaniments.

The change produced in the quinine in all probability represents, in part at least, that which takes place in the 23 to 93 per cent. (*vide* p. 251) of the ingested quinine which disappears in the human body—apparently without any abnormal substance appearing in the urine. Since nothing whatever is known about the metabolites of quinine in man or animals and it is conceivable that one or other of them is actively therapeutic in malaria or concerned, directly or indirectly, with the genesis of blackwater fever, a study of 'hepatized quinine' may have practical importance in medicine as well as chemical and physiological interest.

Owing to the slower rate of conversion which follows the rapid initial rate, we have in most experiments added only minute amounts of quinine, and do not know certainly whether large amounts can be changed *in vitro* or not. But although minute chemically the quantities disappearing are very considerable physiologically, if we assume that the living organ can regenerate the active agent or otherwise maintain the reaction at its rapid initial rate. Selecting Experiment A as showing the highest rate of conversion, it is seen that a 0.8 per cent. NaCl extract of 15 grams of guinea-pig's liver converted certainly not less than 6 mgms. of quinine in 90 minutes; this would represent for 1.36 kilos of human



liver a conversion of 11.2 grams (180 grains) of quinine sulphate (73.5 per cent. alkaloid) in twenty-four hours.

In all the experiments quinine was added in solution as the hydrochloride—the quantities stated indicate pure alkaloid. The estimations were made nephelometrically on quinine isolated by the ammonium sulphate process.

EXPERIMENT A. Guinea-pig, dead five minutes. 15 grams of pulped liver were shaken with 100 c.c. of 0.8 per cent. NaCl solution and strained through muslin. 10 mgms. of quinine were added to the strained liquid and samples of this were taken at once and after one and a half hours incubation at 37° C. Strict aseptic precautions were observed throughout, and no bacteria could be discovered microscopically at the end of the experiment.

1. Boiled at once.	Found 7.7 mgm.	Loss, 23 %
2. Kept at 37° for 1½ hours.	„ 1.85 mgm.	„ 81 %

EXPERIMENT B. Guinea-pig, dead three hours. 20 per cent. liver emulsion in 0.8 per cent. sodium fluoride solution (as antiseptic) strained through muslin. 10 c.c. mixed at once with quinine. Another 10 c.c. kept at 37° for twenty-four hours before addition of quinine. Both were alkaline to litmus throughout.

	Incubated	Q. found	Loss %
1. 10 c.c. fresh emulsion + 0.5 mgm. Q.	43 hours	0.06	88
2. 10 c.c. stale „ + „	72 „	0.38	24

EXPERIMENT C. Guinea-pig, dead nineteen hours. 20 per cent. emulsion in NaF as in B. To two 10 c.c. lots of emulsion added 0.25 mgm. of quinine, one lot in a narrow test-tube, the other in a wide bottle, through which cotton-filtered air was aspirated so as to play on its surface as a strong jet. Both at laboratory temperature.

1. Found after 20 hours.	0.20 mgm. Q.	Loss, 20 %
2. Found after 20 hours.	0.13 mgm. Q.	„ 47 %

Whether the beneficial effect of the jet of air was due to mechanical disturbance, removal of prejudicial volatile matter, or to extra supply of oxygen, remains to be seen.

EXPERIMENT D. Same guinea-pig as C. 10 grams of liver-pulp were shaken with 25 c.c. of 50 per cent. alcohol and filtered under suction through a compact layer of kieselguhr sandwiched between two filter papers. The filtrate was rich in

coagulable protein, yellow, and perfectly clear. Two lots each of 2 c.c. + 10 c.c. of 0.8 per cent. NaF were taken. Both were kept at 37° for twenty-two hours after addition of 0.25 mgm. of quinine.

- |   |                |            |
|---|----------------|------------|
| 1. Boiled a few seconds before addition of Q. | Found 0.245 Q. | Loss, 10 % |
| 2. Not boiled.                                | „ 0.15 Q.      | „ 40 %     |

EXPERIMENT E. Ox-liver three hours after death. 20 per cent. emulsion in 0.8 per cent. NaF, decanted after ten minutes standing. 10 c.c. of the turbid suspension and 0.5 mgm. of quinine were used in each experiment. All were incubated at 37°C. Even after three weeks no putrefaction was noticeable.

Addition other than Q.	Reaction throughout	Treatment	Hours at 37°	Mgm. Q. found	% Loss
1. 10 cc. of 0.8 % NaCl	Alk.	...	20	0.010	- 98
2. 10 c.c. of 0.8 % NaCl	Alk.	Boiled at once	20	0.043	- 14
3. Nil	Alk.	Filtered through paper	20	0.033	- 94
4. 10 c.c. of 0.4 % HCl	Acid	...	20	0.18	- 64
5. 10 c.c. sat. NaCl Sol.	Alk.	...	70	0.52	- 4
6. 10 c.c. sat. Am <sub>2</sub> SO <sub>4</sub>	Acid	...	20	0.48	- 4
7. 10 c.c. of 1 % Sod. Arsenite	Alk.	...	70	0.33	- 33
8. ½ c.c. of Chloroform	Alk.	...	90	0.204	- 59
9. ½ c.c. of toluene	Alk.	...	90	0.42	- 14
10. Nil	Alk.	Boiled at once	7 days	0.40	- 20
11. Nil	Alk.	90° for 3 min.	7 days	0.39	- 32
12. Nil	Alk.	40° for 3 min.	7 days	0.18	- 64

EXPERIMENT F. Guinea-pig killed seventy-five minutes after an intraperitoneal dose of 50 mgms. quinine.

The liver was rinsed in dilute salt solution after excision and wiped dry. Strict asepsis throughout.

- |   |                 |
|---|-----------------|
| 1. Solid liver as removed. (1 gram.)            | = 0.142 mgm. Q. |
| 2. Solid liver kept at 37° for 18 hours         | = none.         |
| 3. Emulsion in 2 % NaF kept at 37° for 18 hours | = none.         |

The spleen (1 gram containing 0.212 mgm. quinine) and kidney (1 gram = 0.244 mgm. quinine) did not lose the whole of their quinine when similarly treated—the quantities left were not estimated.

EXPERIMENT G. Rabbit's liver. 20 per cent. emulsion in NaF as in E. To 10 c.c. of the strained emulsion 0.5 mgm. of quinine was added.

1. Boiled at once.	Mgm. Q. found 0.45	Difference, 10 %
2. Kept at 37° for 3 hours.	„ „ 0.20	„ 60 %

EXPERIMENT H. Sheep's blood, defibrinated at once, 10 c.c. mixed with 0.05 mgm. of quinine and kept in at 37° for three days till putrid. Found 0.048 mgm. No appreciable conversion.

The following conclusions may be drawn concerning the conversion of quinine by liver emulsions\* in vitro:—

1. After short exposure to a boiling temperature the rate of conversion is very greatly reduced—possibly completely abolished, but more evidence is necessary.

2. In the presence of much NaCl or  $\text{Am}_2\text{SO}_4$  no quinine is converted.

3. A moderately strong acid reaction does not prevent the change.

4. It occurs in presence of chloroform, NaF, or sodium arsenite, though less rapidly than in their absence. Toluene is very prejudicial.

5. The active agent is extracted by 50 per cent. alcohol, and in such extract can pass through a fine filter; it is probably thermolabile. It 'deteriorates' considerably in a 0.8 per cent. NaF solution (reaction alkaline) during twenty-four hours standing at 37°C.

6. The facts strongly suggest that it is an enzyme, a 'quininase', but further evidence is essential.

### QUINOTOXIN

It has been shown by H. C. Biddle (1) that short boilings of an aqueous solution of quinine in the presence of feeble acids, such as acetic acid, results in a yellowing of the solution and the formation of appreciable amounts of quinotoxin. B. F. Howard and O. Chick (6)

\* We have learnt since completing this paper that liver emulsions have been shown to destroy Atropin also, (v. CLARK (1913)).

have shown that moist crystals of quinine bisulphate are similarly affected at temperatures above 60°C.

For the frequent assumption that the yellowing which results from the action of light on quinine is also attended by formation of quinotoxin, there appears to be no satisfactory evidence.

We have thought it worth while making observations on this alkaloid for two reasons. Firstly, it is conceivable that the quinine which is metabolized in the human body is transformed into quinotoxin as its first downward step, and also that the therapeutic effects of quinine in malaria, or some of its toxic effects, among them possibly blackwater fever, might be connected, directly or indirectly, with quinotoxin, or some metabolite thereof, rather than with quinine itself. Secondly, we have been unable to discover in the literature that any observations have been made of the effects of pure quinotoxin on man, while even on experimental animals they appear to have been remarkably few. Hildebrandt (5) concerned himself mainly with cinchotoxin, and his only statements on the effects of quinotoxin on higher organisms are that it differs from cinchotoxin in that it is less poisonous and does not produce convulsions in warm-blooded animals.

Our attempts to prepare an adequate quantity of the pure substance by Pasteur's and by Biddle's methods proved extremely troublesome, owing to the readiness with which it underwent partial change into a pigmented substance and to the difficulty of applying adequate criteria of purity. We are correspondingly grateful to Messrs. Howards and Sons for kindly presenting us with a liberal sample prepared by Mr. David Howard forty years ago from the uncrystallisable residues of cinchona bark, and shown by him to be identical with Pasteur's compound prepared by melting quinine bisulphate. It gave the Thalleioquin test as delicately as quinine. With Christensen's Herapathite reagent, it gave black oily globules, but very rarely any crystals of Herapathite, and these only in such minute amount as to suggest they were due to a very minute trace of quinine. Evaporated to dryness with excess of dilute hydrochloric acid for three hours on a water bath, as in Elvove's titration method (8), it 'fixed' exactly the same amount of the acid as did quinine. Titrated by Gordin's method we got variable results which suggested that the method was not applicable

to this alkaloid. - From alkaline watery media, it was not so readily extractable by ether as quinine, and for quantitative extraction we found it necessary to saturate the solution with ammonium sulphate. It gives the Tanret turbidity test—with greatly enhanced delicacy (limit of dilution about 1 in 1 million) in solutions saturated with  $\text{Am}_2\text{SO}_4$ . It can be estimated nephelometrically in the same way as quinine, though with less delicacy.

We have found by taking the alkaloid ourselves that with doses up to 200 mgms. (3 grains) once a day by the mouth no appreciable results followed except an increased feeling of 'bien être' such as a small dose of quinine often produces, and a slight looseness of stools. One of us reached 390 mgms. (6 grains) without other effects. One of us vomited forty-five minutes after a dose of 260 mgms. (4 grains), and diarrhoea followed. We are disposed to regard it as an intestinal or gastro-intestinal irritant.

Free quinotoxin was excreted in the urine and recognizable by the Thalleioquin test applied to the extracted alkaloid and by the yellow colour of its solution in HCl. It did not give Herapathite crystals. Whether the whole amount ingested can be recovered from the urine we have not ascertained. But we have found that liver emulsions, even in presence of NaF, attack quinotoxin—a fact which strongly suggests that the living body is as capable of dealing with quinotoxin as it is with quinine.

EXPERIMENT I. A 20 per cent. emulsion of ox liver in 0.8 per cent. NaF was prepared, and to 30 c.c. of it was added 1.5 mgm. of quinotoxin dissolved in  $1\frac{1}{2}$  c.c. of dilute HCl. After three hours at  $37^\circ\text{C}$ . 86 per cent., and after forty-eight hours 92 per cent., had disappeared.

EXPERIMENT II. A similar emulsion of guinea-pig's liver was filtered. To 10 c.c. lots of filtrate, 0.25 mgm. of quinotoxin were added. In three hours at  $37^\circ\text{C}$ . 64 per cent. had disappeared, in twenty-two hours 68 per cent.

The therapeutic use of quinotoxin in malaria has been investigated by Professors Stephens and Yorke and their colleagues. Their report will be found on p. 217 of the present issue. They show that with a dose of 10 grains on each of two consecutive days, an amount which in the case of quinine would have had very definite effects on the blood parasites, quinotoxin has no appreciable effect.

This result suggests *prima facie* that either it is not a metabolic product of quinine in the human body at all, or that it is quinine itself, or some metabolite along a path which does not include quinotoxin, which is therapeutic in malaria. The question whether quinine is, or is not, metabolized through a quinotoxin stage, and the subsidiary questions bound up with it, nevertheless remain open—*endogenous* quinotoxin may operate very differently.

#### PARTITION OF QUININE BETWEEN BLOOD AND TISSUES

Any exact knowledge of the relative concentrations of a medicinal alkaloid in the blood and various tissues must have a high degree of physiological and physico-chemical interest. The experiments recorded below, although few in number and furnishing the mere beginnings of such knowledge, bring out several significant points.

The quinine was extracted from all the tissues except brain by the ammonium sulphate method, from brain by the alcohol method, and in both cases estimated nephelometrically. The results with the liver are too low, owing to the rapid modification or destruction of quinine which takes place in this tissue even post-mortem. If such loss occurs in other tissues at all, it occurs less rapidly, and has been, we believe, negligible under the conditions of our experiments, since the control estimates given above were made under very similar conditions.

The only observations found in the literature on quinine in the tissues are those of Giemsa and Schaumann (3) on dogs and guinea-pigs dosed with this drug. Although made by rough comparisons of the results of qualitative tests applied to the quinine extracted from different weights of the tissues investigated, they create a strong presumption that quinine is present at higher concentrations in the tissues (especially in the suprarenal glands) than in the blood.

EXPERIMENT I. Guinea-pig, 400 grams in weight, 0.5 grams of quinine dissolved in 10 c.c. of water and enough HCl to effect its solution was injected into the peritoneal cavity. Forty-five minutes later the already moribund animal was killed. Blood was taken from the heart, defibrinated, and centrifugalised—the quinine-content of the serum and corpuscles (unwashed) was determined

separately. Each of the organs investigated was rinsed free from peritoneal fluid by salt solution and wiped dry before it was weighed.

	Taken	Mgms. Q. found	Mgms. Q. in 100 c.c.
Blood serum	2.6 c.c.	0.1326	5.1
Blood corpuscles	2.2 c.c.	0.033	1.5
			Mgms. Q. in 100 grams
Blood, S.G. 1050	...	...	3.285 calculated
Liver	20.48 grams.	14.85	73
Two kidneys	3.87 "	4.025	104
Two suprarenals	0.36 "	7.92	2200

The yield of the suprarenals was so immense as to rouse a suspicion that the method of estimation might give excessive results in glands containing adrenalin. We have, however, ascertained that addition of adrenalin to a quinine solution does not affect the accuracy of the estimation, and that pure adrenalin solution or fresh adrenal glands put through the process yield nothing to ether which will give turbidity with Tanret's reagent. We must, therefore, regard the 2.2 per cent. of quinine as having been actually present.

EXPERIMENT II. Guinea-pig, female, weighing 420 grams. Quinine 50 mgms. into peritoneal cavity. No notable symptoms resulted. Killed seventy-five minutes later.

Post-mortem, the spleen and the liver were acutely congested.

	Grams of tissue taken for estimation	Mgms. of Q. found therein	Mgms. of Q. in 100 grams
Blood	4.086	0.0642	1.6
Spleen	3.957	0.84	21.2
Liver	3.015	0.428	14.2
Kidney	1.697	0.414	24.1
Muscle	0.579	0.357	6.2
Suprarenals	0.305	0.492 +	161.0 +

In the suprarenal estimation the quinine extract was lost after the preliminary rough estimation; the result given above is a minimal one.

EXPERIMENT III. Buck rabbit, weighing 2.2 kilos. 10 c.c. of solution containing 400 mgms. of quinine and enough HCl to dissolve it was injected into the auricular vein. The injection was barely complete when the animal unexpectedly died. Blood taken within three minutes of the injection from the superior vena cava was found to contain 40 mgms. of quinine per 100 c.c. Reckoning the blood volume (by Dreyer's formula for rabbits  $= \frac{W^{\frac{2}{3}}}{1.576}$ ) as 107 c.c. it would have contained 374 mgms. per 100 c.c. had no quinine left the circulation. It is not very probable, in view of its source, that the blood sample was truly representative of the blood generally, but it is clear that 90 per cent. of its quota of quinine had disappeared within three minutes.

EXPERIMENT IV. Buck rabbit of 1790 grams. Quinine 200 mgms. into peritoneal cavity. No special symptoms except early restlessness and rapid breathing followed by quietness and some prostration. Killed after seventy-five minutes. Tissues removed at once, rinsed, wiped dry and placed in weighed flasks containing acidulated saturated  $\text{Am}_2\text{SO}_4$  vols.

Tissue.					Mgms. of Q. in 100 grams.
Blood	...	...	...	...	1.45
Liver	...	...	...	...	1.26
Kidney	...	...	...	...	7.0
Muscle	...	...	...	...	3.1
Suprarenals	...	...	...	...	5.5
Brain (sample of whole)	...	...	...	...	0.8
Fat (infra-sternal)	...	...	...	...	1.24
Peritoneal fluid	...	...	...	...	3.12

Fifteen c.c. of peritoneal fluid were obtained (yellow, highly albuminous and turbid, with masses of desquamated endothelium and leucocytes). Of the 200 mgms. of quinine introduced into it certainly less than 1 milligram remained.



The low quinine-content of the adipose tissue may possibly be due to non-attainment of equilibrium with that of the blood-plasma, since this tissue has a poor blood supply. That the partition-coefficient of quinine between fat and blood-plasma or lymph is not strongly, if at all, in favour of fat is however indicated by the rapid effectiveness of intramuscular injections of quinine dissolved in oil. The low finding in brain is, in view of its rich blood supply, not at all likely to be due to non-attainment of equilibrium.

### CONCLUSIONS AND COMMENTS

1. The concentration of quinine in normal red blood-corpuscles is very much less than in the surrounding plasma. The difference shown in Experiment I is, owing to inadequate separation of corpuscles from adherent serum, certainly not high enough. The ratio  $\frac{\text{Serum Q.}}{\text{Corpuscles Q.}}$  exceeds  $\frac{3}{1}$ .

2. The concentration of quinine in most of the tissues is very much greater than in blood, *v. ratio*  $\frac{\text{Tissue Q.}}{\text{Blood Q.}}$  in the following table:—

	EXPERIMENT I		EXPERIMENT II		EXPERIMENT IV	
	Guinea-pig		Guinea-pig		Rabbit	
Mgms. Q. per 100 grams of body weight	125		12		11.1	
Minutes after dose	45		75		75	

Tissue	Mgms. Q. in 100 grams	$\frac{\text{Tissue Q.}}{\text{Blood Q.}}$	Mgms. Q. in 100 grams	$\frac{\text{Tissue Q.}}{\text{Blood Q.}}$	Mgms. Q. in 100 grams	$\frac{\text{Tissue Q.}}{\text{Blood Q.}}$
Blood	3.285	...	1.6	...	1.45	...
Suprarenal	2200	700	162	100	5.5	3.8
Kidney	104	35	24	15	7.0	4.8
Spleen	...	...	21	13.2	...	...
Liver	(73)	(22)	(14)	(8.7)	(1.26)	(0.87)
Muscle	...	...	6	3.8	3.1	2.1
Adipose	...	...	...	...	1.24	0.8
Brain	...	...	...	...	0.8	0.55

3. With guinea-pigs, enormous concentrations of quinine occur in the suprarenals. The facts recorded by Giemsa and Schaumann strongly suggest that this will prove to be true for dogs also. The absence of any such preponderant accumulation in the rabbit of Experiment IV is no sufficient reason for doubting that it will be found true for rabbits also—this particular rabbit had already disposed of most of the quinine given. Assuming it to be true for man, it may perhaps be correlated with the symptoms of suprarenal inadequacy sometimes observed in malarial patients, more frequently by French physicians.

4. The contrast between the quinine-content of the tissues of the rabbit in Experiment IV and the guinea-pig of Experiment II is a remarkable one. The animals had received intraperitoneally nearly the same dose per 100 grams of body-weight at the same interval before death, and the quinine content of the rabbit's blood was not much less than that of the guinea-pig. As the observations on the peritoneal fluid leave no doubt that the rabbit at least had absorbed all but 1 mgm. of the alkaloid injected, and since not one of its tissues had as high a quinine-content per 100 grams as the dose administered per 100 grams of body-weight, it is certain that a very large proportion of the quinine had already been excreted or metabolized—a very much larger proportion than in the guinea-pig. The contrast may possibly be dependent on the difference of species. Contrasts quite as considerable will, however, be seen later between different men.

#### QUININE CONTENT OF HUMAN BLOOD AND URINE

The cases investigated are classified according to the dose of quinine and the details of its administration. All were military patients with simple tertian malaria and well habituated to the drug for many months, except where otherwise stated.

The letter T in the columns headed 'malarial parasites' indicates Trophozoites and the letter G Gametes, these facts being kindly supplied to us by Professors Stephens and Yorke and their colleagues. In every case, except where otherwise stated, the blood on the third day of quinine medication was free from parasites.

PATIENT 1, P. A., aet. 20. Intermittent pyrexia (trench-fever?). Not habituated to quinine.

Dose: First day, 15 grains of quinine sulphate in solution by mouth every three hours, 6 a.m. to 9 p.m. On the two or three occasions when patient vomited the dose, a similar amount was given again. His total intake on this day was therefore probably much more than 90 grains, since absorption is usually rapid.

Second day, 15 grains of quinine hydrochloride by intramuscular injection every three hours from 6 a.m. to 9 p.m.

Total alkaloid ingested > 9070 mgms., total excreted in urine, 1643 mgms. There was diarrhoea and vomiting both days. The faeces of the second day contained more than 100 mgms. quinine.

	Max. Temp.	Mgms. Q. per litre Blood		Mgms. Q. per litre Urine		Ratio $\frac{\text{Urine Q.}}{\text{Blood Q.}}$		Hours excretion after last dose
		1 p.m.	10 p.m.	1 p.m.	10 p.m.	1 p.m.	10 p.m.	
Day 1	101·8°	7·85	8·23	600	1100	76	133	121
Day 2	100·6	8·0	6·4	2000	2200	250	390	
Day 3	100·6	...	...	...	...	...	...	
Day 4	99·6	2·6	...	300	...	115	...	

The excretion of quinine in urine at a concentration three hundred and ninety times as great as that in the blood is probably unique as an instance of the 'secretory power' of the kidney—it is much greater than has been observed with any of the normal constituents of urine which we have found on record.

GROUP A, aet. 20 to 36 years.

Dose: 15 grains of quinine sulphate ( $73\frac{1}{2}$  per cent. alkaloid) in solution, at 6, 9, 12 a.m. and 3, 6, 9 p.m. on each of two successive days.

The first six cases of the group are strictly comparable, if we treat as negligible the small losses of quinine in the stools of 2 and 4.

In Case 8, even on the third day at 1 p.m. (twenty-seven hours after the last dose) the amount of quinine per litre of blood was still considerable—8·3 mgms. Malarial parasites could no longer be found. It is remarkable, in view of the very much larger amount of quinine in his blood, that the parasites persisted longer than in most of the other patients—possibly it is not the quinine which is

Patient	Max. Temp.		Mgm. Q. per litre Blood				Malarial parasites in blood		Mgm. Q. in urine	% Q. excreted	Hours excretion after last dose
			1st day		2nd day.		1st day	2nd day			
	1st day	2nd day	1 p.m.	10 p.m.	1 p.m.	10 p.m.					
2 HU	102.8°	103.2	3.8	4.5	2.2	2.0	T.	O.	487	6.8	154
4 MO	98	98	3.3	...	1.0	2.2	T.	O.	...	...	...
5 PO	98.4	97°	1.6	2.0	1.0	4.4	T.G.	O.	...	...	...
6 MI	100.6	99	5.5	5.0	2.5	5.0	T.G.	O.	...	...	...
7 RY	97	97	3.57	3.0	3.3	13.3	T.	O.	574	6.7	111
8 WA	99.4	104	16.6	16.6	16.6	16.6	T.G.	T.	913	10.6	187
9 SH	102	98	11.1	4.5	2.1	6.6	T.G.	O.	203	(2.4+)	128
10 DO	100	100	1.0	5.5	6.6	10.0	T.G.	T.G.	648	(7.5+)	133

present but the quinine which has disappeared (i.e. one of its metabolites) which is obnoxious to the parasites.

In Case 2 the quinine of each specimen of the urine passed after 6 a.m. on the first day until 7.15 p.m. on the fourth day, when quinine ceased to be excreted, was estimated separately. Graph I, p. 254, shows the results obtained. Getting, by interpolation the concentration of the urine at the times when the blood samples were taken, the  $\frac{\text{Urine Q.}}{\text{Blood Q.}}$  ratio is obtained.

CASE 2.								Mgm. Q. per litre urine	$\frac{\text{Urine Q.}}{\text{Blood Q.}}$
1st day	1 p.m.	...	...	...	...	...	...	95	25
,,	10 p.m.	...	...	...	...	...	...	105	23
2nd day	1 p.m.	...	...	...	...	...	...	170	80
,,	10 p.m.	...	...	...	...	...	...	130	75

In Cases 9 and 10 the losses by vomiting are unknown and may have been considerable.

Attention is called to the following points:—

1. The great differences of concentration of blood-quinine in the different cases—presumably due to differences either in the rate of metabolism of quinine or in the rate of its excretion.

2. The association of a high quinine-content of blood ( $> 11$  mgms. per litre) with symptoms of quinine intoxication. In Case 8, W. A., with 16.6 mgms., these were so severe throughout that administration of stimulants was often necessary. This association was specially striking in Case 9, with 11 mgms. at 1 p.m. and only 4.5 mgms. at 10 p.m. From 9 a.m. to 6 p.m. the patient was suffering severely with headache, prostration, nausea, rapid pulse, and buzzing in the ears. After this his condition rapidly improved, and next day he was quite comfortable. Case 7 reached 13.3 mgms. per litre of blood only at the end of the period, and possibly maintained this only for a short time, but unfortunately we have no record of his symptoms.

3. The association of the persistently high quinine-content of the blood in Case 8 with marked urobilinuria. In no other case, except with actual blackwater fever, has there been any increase of urobilin, although many have been feverish. Since urobilinuria is a common precursor of the haemoglobinuria of 'blackwater,' its appearance in this case is suggestive of some increased haemolysis due directly or indirectly to quinine.

PATIENT 13, K. N., aet. 35.

Dose: First day, 30 grains quinine sulphate at 10 a.m. and 15 grains at 1, 4 and 7 p.m. Total 75 grains.

Second day, 15 grains every three hours, 6 a.m. to 9 p.m. Total 90 grains. Vomited at 11 p.m. on first day. Total quinine 7880 mgms. alkaloid less amount lost in vomit.

No diarrhoea and only one stool (containing a negligible trace of quinine).

Max. Temp.		Mgm. quinine per litre of blood.				Malarial parasites in blood	
		1st day		2nd day			
1st day	2nd day	1 p.m.	10 p.m.	1 p.m.	10 p.m.	1st day	2nd day
100.2°	99.2°	1.6	2.0	6.6	7.2	T.G.	T.G.

## GROUP B.

Dose: 15 grains quinine sulphate in solution by mouth every four hours, beginning at 10 a.m. on first day. No vomiting or diarrhoea.

Total quinine sulphate before 1st blood sample 15 grains.

" " " " 2nd " " 45 "  
 " " " " 3rd " " 105 "  
 " " " " 4th " " 135 "

Patient	Max Temp.		Mgm. Q. per litre Blood				Malarial parasites in blood	
			1st day		2nd day			
	1st day	2nd day	1 p.m.	10 p.m.	1 p.m.	10 p.m.	1st day	2nd day
11 JOI	98.4°	98°	0.5	...	1.0	4.0	T.G.	O.
12 OW	104	98.4	0.5	0.6	4.8	9.9	T.G.	T.G.

Case 12, O. W., is the only one, except 17, K. N., whose blood still contained malarial plasmodia (*P. vivax*) on the third day: they were not found on the fourth day.

## GROUP C. INTRAMUSCULAR INJECTIONS.

Both cases had received 30 grains of quinine hydrochloride by mouth and 30 grains by intramuscular injection on each of the twelve days preceding. On the first day of our observations both had received at 4 and 7 a.m. 15 grains quinine salt by mouth, and (the last dose) at 9.30 a.m. 30 grains quinine salt intramuscularly. No vomiting or diarrhoea.

Patient	Age	Max. Temp.		Mgm. Q. per litre Blood		Mgm. Q. per litre Urine		Ratio $\frac{\text{Urine Q.}}{\text{Blood Q.}}$		Hours duration of excretion after last dose
		1st day	2nd day	3 hours after last dose	27 hours after last dose	3 hours after last dose	27 hours after last dose	3 hours after last dose	27 hours after last dose	
14 DA	21	98.4°	98.4°	3.23	1.97	337	255	104	129	115
15 JOW	29	98.4	99.2	1.98	1.42	168	79	85	56	107

Malarial plasmodia were absent on both days.

## GROUP D. SMALL DAILY DOSES.

5 grains of quinine sulphate (238 mgms. alkaloid) orally, in solution, every morning, except Sundays, at 9 a.m. during the three weeks preceding the Thursday on which the blood and urine were sampled.

Patient	Mgms. Q. per litre, blood, 3 hours after last dose	Mgms. Q. per litre of Urine	Urine Q. Blood Q.
17 KN ... ..	2.3 (12.30 p.m.)	73.3 (1.15 p.m.)	31.8
18 TO ... ..	1.6 „	22 (12.30 p.m.)	13.6
19 BU ... ..	1.9 „	18.65 (1.15 p.m.)	9.8

In Case 17, K. N., malarial parasites were present in the blood every day; they were absent in Case 18, T. U., and Case 19, B. U., although the quinine content of the blood was decidedly lower.

## GROUP E. INTRAVENOUS INJECTIONS.

A solution of quinine hydrochloride (81.6 per cent. alkaloid) was injected into the median basilic vein of one arm, and a sample of blood was then as quickly as possible (certainly within one minute) withdrawn from that of the other arm.

	Mgm. Q. alkaloid injected	Mgms. Q. if distributed equally through 3 litres of blood	Mgms. Q. per kilo injected	Found Mgm. Q. per litre blood (S.G. 10607)	% Q. disappeared from blood
20	530	177	7.5	44.2	77
21	530	177	7.5	23.6	87
22	480	160	6.8	16.6 and 3 hours later 4.42	90

In Case 22 a sample of urine 25 c.c. passed fifty minutes after injection of the quinine contained 240 mgms. per litre. Assuming a linear drop in concentration of quinine in the blood, although it would doubtless be much more rapid, this would give a minimum  $\frac{\text{Urine Q.}}{\text{Blood Q.}}$  ratio of  $\frac{240}{13.2} = 18$ , or a maximum of  $\frac{240}{4.42} = 54$ .

The excretion time was sixty-six hours, as judged by the fact that the urine then ceased to give the Herapath test.

Total quinine excreted in 2400 c.c. urine was 17.9 mgms.

Percentage excreted  $\frac{179}{480} \times 100 = 37.3$ .

CASE 16, M. X., act. 29. Malignant tertian (*Plasmodium falciparum*).

*First attack of blackwater fever.*

Date	Max. Temp.	15 grain dose of sulphate Q. by mouth	Mgm. Q. in litre blood	Malarial parasites	Mgm. Q. in litre urine	Urine Q. Blood Q.
12.4.18	100 F	At 2, 6, and 10 p.m.	...	T.G.	...	...
13.4.18	103	At 9 a.m. (vomited soon after)	13.3 (at 12.30 p.m.)	T.G.	12.5 (at 12.30 p.m.)	0.94
14.4.18	98.4	Nil.	...	...	...	...

Haemoglobinuria began at 4 p.m. on 12th April, two hours after the last dose, and lasted thirty-two and a half hours till 12.30 p.m. on the 13th April.

The quinine-content of the blood on the 13th April is a very large one for such a dose of quinine at such an interval from the dose, especially as the last dose was vomited soon after it was given.

The ratio  $\frac{\text{Urine Q.}}{\text{Blood Q.}}$  is unique in our observations. It is the only one not showing quinine in the urine at considerably greater concentration than in the blood. It is evident that the power of the kidney to excrete quinine was greatly diminished.

*Second attack of blackwater fever.*

Date	Max. Temp.	15 grain doses of Q. sulphate by mouth	Malarial parasites	Vomited	Mgm. Q. in litre blood	Mgm. Q. in litre urine	Urine Q. Blood Q.
24.5.18	...	At 10, 2 and 6 p.m.	...	0	...	...	...
25.5.18	104°	At 10 a.m. and 2 p.m.	...	6 times	...	...	...
26.5.18	98	Nil.	...	...	1.19 at 1 p.m.	18.68	15.6



Haemoglobinuria began at 5.45 p.m. on the 25th May (three and three-quarter hours after the last dose of quinine), and lasted till 10.30 p.m. of the same day—altogether four and three-quarter hours. Urobilinuria lasted twenty-one hours. As the urobilin was disappearing an abnormal pigment not further investigated made its appearance and coloured the precipitate produced in Schlesinger's urobilin test (addition of an equal volume of 10 per cent. alcoholic zinc acetate solution to the urine) a salmon pink—this phase lasted thirty-two hours. Acetone and diacetic acid were absent.

The points of special interest in these two attacks are the low  $\frac{\text{Urine Q.}}{\text{Blood Q.}}$  ratio during the first attack, and the fact that even on the day after a second milder attack, this ratio, although showing a considerable return of the secretory power of the kidney, is still much less than it would be in any normal patient.

It is an interesting question whether the defect in the secretory power of the kidney for quinine was a primary condition, and the large amount of quinine in the blood resulting therefrom the cause of the haemolysis, or whether the haemolysis occurred first and by diminishing the excretory functions of the kidneys for quinine was ultimately responsible for the high quinine-content of the blood. That the functions of the kidneys in secreting some at least of the other constituents of urine were not seriously impaired during the 'blackwater' period is shown by the high secretion-rate of 7.6 c.c. per minute which was observed.

The secretory activity of this patient's kidneys was also investigated (by the phenol-red test) in a non-haemoglobinuric period intervening between the two attacks of blackwater fever. 72 per cent. of the phenol red administered was found in the urine in the first two hours—evidence, so far as any one test can supply it, of good renal function.

The rate of excretion of quinine was also investigated during this normal period. On April 26th, at 2 p.m., a solution of 45 grains of quinine sulphate (2150 mgms. alkaline) was administered orally.

After fifty-five hours the Herapath test was no longer obtainable from 40 c.c. of urine.

The total quinine excreted in the fifty-eight hours was 487 mgms. = 22 per cent. of the quinine administered.

Graph II, p. 255, shows the Rates of excretion of Urine and of Quinine and the concentration of quinine in the excreted urine. Apart from the initial rise in quinine concentration, it will be seen that almost every increase in the rate of excretion of urine is attended by a reduction in the concentration of the quinine in the urine.

### QUININE IN FAECES

There is a general consensus of opinion that after the administration of solutions of quinine in moderate doses the amount which is excreted with the faeces is so small as to be negligible.

One of us after a dose of 30 grains of the hydrochloride on each of two consecutive days was unable to detect even a trace in his faeces by a method which would have yielded a positive result with as little as 0.1 mgm. of quinine in 10 grams of faeces.

Of the men taking 90 grains of the sulphate (4300 mgms. alkaloid) on each of two consecutive days, only those rendered diarrhoeic thereby produced faeces in which quinine could be detected in more than traces.

In Case 2, Group A, the 218 grams of semi-fluid faeces of the first two days yielded only 24 mgms. of quinine as estimated by the 'minimal' method described earlier—and could hardly have contained more than 50 mgms. (= 0.6 per cent. of the 8600 administered). In Case 1, where many fluid stools were passed, the amount was much greater—the faeces of the first day were lost, but those of the second day contained at least 100 mgms. quinine—probably at most 200 mgms.

In Cases 4, 11 and 13, with normal stools the amount of quinine was so small that it was impossible to get crystals of Herapathite from them. When the stools have not been 'loose,' we have therefore felt justified in assuming that excretion by the faeces was negligible.

### INTERVAL BETWEEN DOSE OF QUININE AND APPEARANCE IN URINE

Unless catheterization be resorted to, only 'maximal results' can be obtained. Examining urine passed naturally by eighteen healthy

men each of whom had taken a solution of 0.33 gram (5 grains) of quinine sulphate on an empty stomach, the times obtained were:—

8 minutes	...	...	...	1 case.
10 "	...	...	...	1 "
18 "	...	...	...	11 cases.

With five men taking 15 grains of quinine sulphate in solution on an empty stomach, quinine appeared in the urine passed after the following intervals:—

9 minutes	...	...	...	1 case.
10 "	...	...	...	1 "
12 "	...	...	...	1 "
14 "	...	...	...	2 cases.

There can therefore be no doubt that quinine administered in solution as the sulphate to fasting men begins to be absorbed, and also to be excreted in the urine, with considerable rapidity.

#### DURATION OF EXCRETION

The number of hours after the last dose of quinine during which it was possible to obtain Herapathite crystals from the ether extract of 40 c.c. of urine has been determined in some of the cases. The end-point would generally correspond to a quinine-content of less than 0.025 mgm., in the 40 c.c. of urine. It is difficult at present to attach much significance to the results.

Single dose taken fasting:—

Mgms. of quinine alkaloid taken orally in solution	Secretion period of last sample of urine containing quinine
100	38—47 hours
100	34—41 "
238 (5 grains of Q. sulphate)	39—45 "
238 (5 grains of Q. sulphate)	52—64 "
238 (8 cases out of 10)	48—60 "
238 (2 cases out of 10)	60—72 "
480 (intravenous)	60—66 "
500	40—41 "
2150 Case 16 MX	50—55 "

It appears probable for single doses taken by the mouth that the excretion-time, although differing greatly with different men, is much the same whether the dose be large or small.

Data of the excretion-period after the last dose of a long series have been recorded with the grouped cases. The longest period was seven and a half days in Case 8, the patient with the highest concentration of quinine in his blood.

#### THE CONCENTRATION OF QUININE IN URINE AND ITS RATIO TO THAT IN BLOOD

In Cases 1, 2, 14, 16 and 22, the maximal concentration expressed as mgms. quinine per litre of urine have been 3000, 200, 255, 219 and 240 respectively. Our facts do not support Nierenstein's (7) statement that 'there is a tendency for the excretion of the quinine passed to reach a concentration of 7 to 11 grains (450 to 650 mgms.) per litre of urine.'

In every case, except 16, during an attack of blackwater fever, the concentration in urine has been, *at all stages* investigated, many times greater than in the contemporaneous blood, the  $\frac{\text{Urine Q.}}{\text{Blood Q.}}$  ratio ranging from 9 to 390. Even with so small a dose as 238 mgms. quinine (5 grains of quinine sulphate as ordinarily prescribed), a ratio of 31 was found three and a half hours after the dose (Case 17).

#### PERCENTAGE OF ADMINISTERED QUININE FOUND IN BLOOD

The maximum percentage was found in Case 17 on the small daily dose of 238 mgms. quinine. Assuming the volume of blood to have been three litres, there was  $\frac{3 \times 2.3 \times 100}{238} = 2.9$  per cent. of the quinine ingested.

#### THE 'ACME' OF EXCRETION

According to Hartmann and Zila (4), this occurs between four and eight hours after oral administration of a single dose of quinine (quantity not known to us). In Case 16, M. X., after a dose of 2150 mgms., during a non-haemoglobinuric period, the maximum excretion rate (0.55 mgm. quinine per minute) as also the maximum

concentration of quinine (219 mgms. per litre), was found in the urine of the period twenty-three to twenty-five hours. Whether a late 'acme' is general with a large dose or was a peculiarity associated with the liability of the patient to blackwater fever remains uncertain.

#### PERCENTAGE OF QUININE EXCRETED

A study of the literature shows that with men taking moderate doses of a soluble salt of quinine, whether by mouth or by intravenous or intramuscular injection, the percentage of the quinine which leaves the body differs greatly in different men, but has never been found less than 23 or greater than 66.

This has been true also of the few cases in which we have ourselves determined the percentage after single doses. We should add, however, that Hartmann and Zila (2) have recently recorded after oral administration a total excretion of 15 to 35 per cent.

With 238 mgms. orally ... we found 23 per cent. (E. W.).  
 „ 480 „ intravenously „ „ 37 per cent. (Case 22).  
 „ 2150 „ orally „ „ 24 per cent. (Case 16).

But with the men of Group A taking very large doses (90 grains a day on each of two successive days) the percentage excreted was unprecedently low.

Case 2, H. U., 6.8 per cent. = 93 per cent. metabolized.  
 „ 7, R. Y., 6.7 per cent. = 93 per cent. „  
 „ 8, W. A., 10.6 per cent. = 89 per cent. „

For a satisfactory explanation of this paradox, a better all-round knowledge of the fate of quinine inside the body and of the rate of its absorption from the alimentary canal under normal and abnormal conditions is essential. The explanation is likely to have much clinical interest.

#### DISCUSSION

1. It is probable that the diminished percentage excretion of quinine by the patients of Group A is bound up with the equally remarkable diminution in the amount of quinine found in the blood of most of them at 1 p.m. on the second day of quinine medication, and also at 10 p.m. in the two cases with abnormal intestinal conditions (Cases 2 and 4).

It is for the light it throws on this question, and also on the functioning of the kidney, that we have thought it desirable to publish Graph I relating to Case 2, the only one of Group A in which the quinine of each sample of urine was estimated separately. That the patients (Cases 2, 4, 5, 6, 7 and 8) did actually ingest the quinine and retain it there is no doubt. That none of the urine was lost we have full confidence.

The quinine of the third, fourth and fifth days' faeces was not estimated, but as these were not loose they were assumed to contain only negligible amounts. There was no stool on the first day, but that of the second day (late evening) was semi-fluid and contained at most 50 mgms. We have very little doubt that the total loss of quinine in the combined faeces of the whole five days was well below 100 mgms.

The total output of quinine in the urine, calculated by summing up the nephelometric estimations of 5 c.c. of each individual sample, was 476 mgms. A gravimetric estimation by the Iodine Potass-Iodide precipitation method described by two of us (1), was made on a representative quarter of the total 5·6 litres of urine of the four days (obtained by mixing together a quarter of each of the seventeen specimens of urine)—found for total urine 484 mgms. quinine, a very satisfactory confirmation of the accuracy of the nephelometric estimations. Allowing 100 mgms. for the faeces, the total quinine leaving the body, expressed as a percentage of the quinine ingested, was  $\frac{584}{8600} \times 100 = 6\cdot78$  per cent.

The figures given below show the quinine excretion in the urine in successive twelve-hour periods:—

CASE 2	Mgm. Q. Ingested	Mgm. Q. excreted in urine
0—12 hours	2866 (60 grains Q. Sulph.)	197
12—24 "	1433 (30 grains Q. Sulph.)	116
24—36 "	2866 (60 grains Q. Sulph.)	112·6
36—48 "	1433 (30 grains Q. Sulph.)	22·8
48—60 "	Nil.	17·4
60—72 "	Nil.	7·0

It will be seen that although in the first twenty-four hours 313 mgms. of quinine was excreted, in the second twenty-four hours not more than 185 mgms. (135 mgms. in urine + 50 mgms. in faeces) left the body, and in the third twenty-four hours not more than 77 mgms. (27 + 50 mgms. in faeces).

To explain this falling off on the second day, it is necessary to assume that either a very much smaller proportion of the quinine ingested was absorbed from the intestine, the unabsorbed residue being partly expelled with the faeces and partly altered by bacteriolytic or other agencies; or as an alternative that absorption was quantitatively normal but a very much larger proportion of the absorbed quinine was metabolized.

Coming to the detailed curves of quinine excretion, attention is called to the interesting fact that, except for the two initial and final samples of urine where quinine was just beginning or ceasing to be available for excretion, every increase or decrease of the rate of excretion of urine was *without exception* accompanied by an increase or decrease of the rate of excretion of quinine (*v.* Graph I), and that very frequently the more rapidly the urine was being secreted the greater was the concentration of the quinine in it.

In Graph II, presenting the results obtained with the patient (Case 16, M. X.) who was subject to blackwater fever, it will be seen that although nearly every increase in the rate of secretion of urine was accompanied by an increased rate of excretion of quinine, the quinine was excreted at a *smaller* concentration.

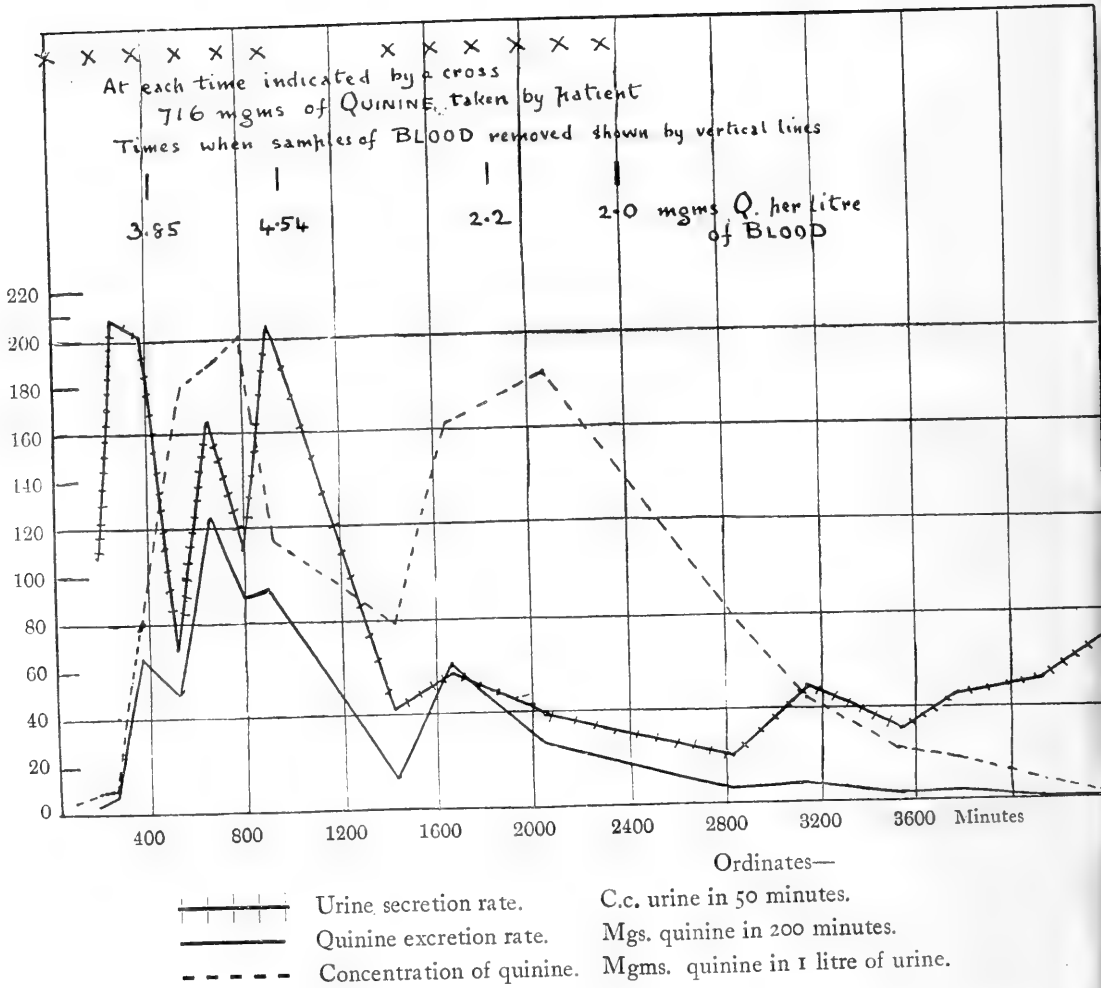
2. The quinine-content of the blood of the various cases subjected to precisely similar medication shows very great individual differences. Compare in Group A, Case 5, with 1·6, 2·0, 1·0 and 4·4 mgms. quinine per litre in the successive samples of blood, and Case 8, with 16·6 mgms. quinine per litre in each sample, even the very first.

The various cases differ greatly, not only in the maximal concentrations attained but also in the rapidity with which the maximum is reached. Further, as has already been pointed out, most of them have less quinine in the third sample than in the first.

These differences in the amount of quinine in the blood are doubtless accompanied by (more or less proportional ?) differences in the concentration of the quinine in the tissues.

GRAPH I.

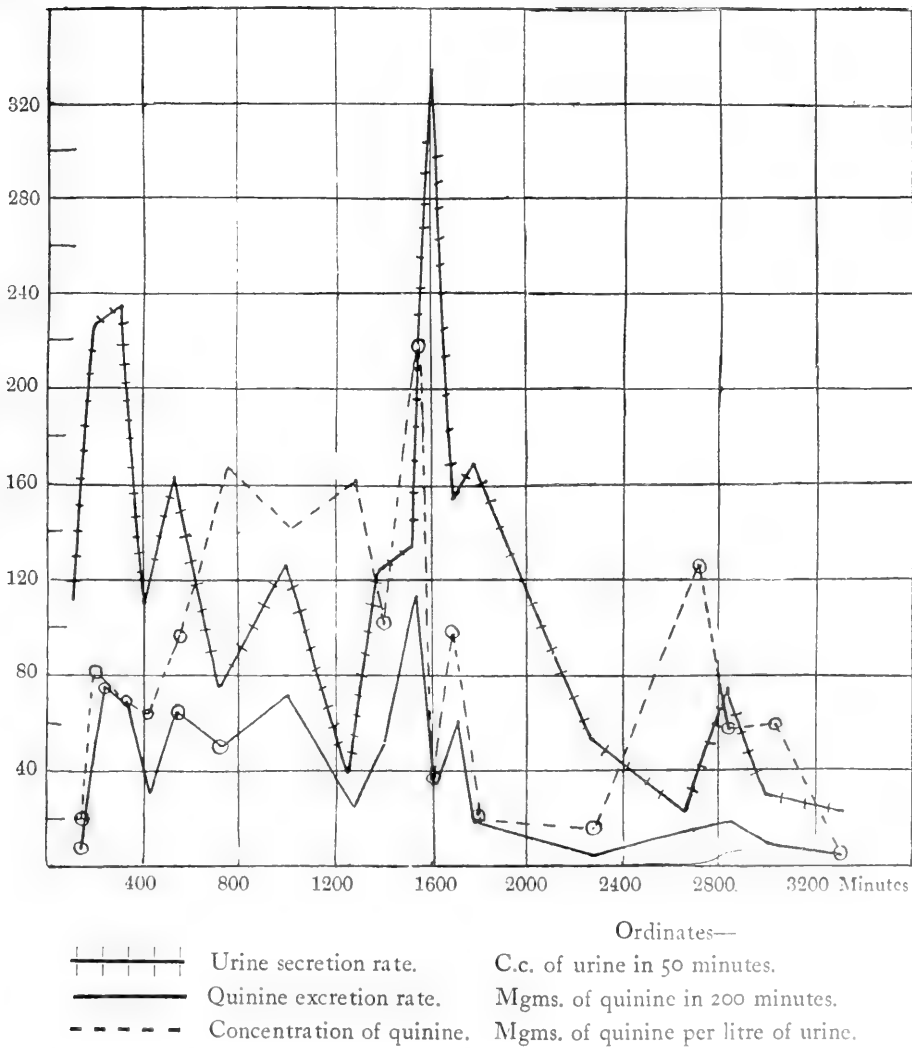
CASE 2. HU.





## GRAPH II.

CASE 16. MX. 2150 mgms. quinine by mouth, as quinine sulphate.



3. Comparing men taking different doses by mouth, it should be noted that one of the patients taking 5 grains of quinine sulphate once each day (Case 17, Group D) attained as high a level of quinine concentrations in his blood three and a half hours after the dose as many of the patients of Group A after they had taken 90 grains (15 grains every three hours).

4. A quinine-content of 2.3 mgms. per litre of blood was in Group D, Case 17, compatible with the continued existence of malarial plasmodia in the blood day after day throughout a period of three weeks.

5. As we are informed that relapse occurred eventually in every one of the malarial cases in which the quinine of the blood was estimated, it is clear that even 16.6 mgms. quinine per litre maintained at a steady level for at least thirty-three hours has not sufficed to prevent a relapse, and therefore that no concentration of quinine in the blood at all likely to be compatible with the continued existence of the host can be counted on to effect a radical cure.

Whether a certain minimum percentage of quinine in the blood may be necessary to cut short a particular attack of malaria is another question.

#### CONCLUDING REMARKS

To the facts recorded concerning quinotoxin we would add that we have seen no reason to suspect its presence in the urine of patients taking quinine—the quinine obtained by the Iodine KI process has always been colourless even though dried at 120° C., or at worst of a very pale lemon tint, and it has given Gordin titration values in close agreement with the gravimetric results. Nevertheless, the possibility that a trace of quinotoxin is present in some cases should be kept in view, although its detection would be by no means easy. As a hypothetical metabolite of quinine it might quite well have a fugitive existence as it arises inside the body.

Further investigation of the changes produced in quinine by liver-extracts appears to us urgently desirable as the most direct means of ascertaining the fate of the 23 to 93 per cent. of the ingested quinine which is metabolized in the body. Our observations

hitherto have had a merely preliminary character. A full knowledge of the metabolism of quinine may well be essential for any adequate explanation of its therapeutic effects and failures.

We are much indebted to Professor Stephens and Professor Yorke for the many facilities they have afforded us in obtaining specimens from malarial patients, and to Professor Yorke for much kindness in making the various intraperitoneal and intravenous injections referred to in the paper.

### RÉSUMÉ

1. Delicate methods are described for the estimation and detection of quinine in animal tissues and liquids.

2. Quinine does not normally suffer change in putrifying urine or faeces.

3. Quinine introduced into an animal in large doses accumulates in most of the tissues at very much higher concentrations than in the blood.

4. Of the quinine present in the blood, more than three-fourths is in the serum (plasma?). Normal red corpuscles take up very little quinine.

5. After intraperitoneal injections the suprarenal glands take up quinine at much higher concentration than any other tissue examined; the kidneys probably come next in the series.

6. The healthy human kidney excretes quinine at much higher concentration than that at which it is present in the contemporaneous blood. During an attack of blackwater fever it appears to lose this power.

7. The liver of rabbits, guinea-pigs and oxen rapidly attacks quinine post-mortem and presumably during life. The properties of the active agent suggest that it is an enzyme. The product or products presumably represent normal metabolites of quinine in the living body.

8. Experiments directed to ascertain whether quinotoxin is a normal metabolite have shown that (*a*) it is attacked by liver extracts; (*b*) when ingested by mouth it produces alimentary disturbances, but some is absorbed and some at least is excreted unchanged in urine;

(c) any anti-malarial action which it may exert is so slight in comparison with that of quinine as to be negligible.

9. A given dose of quinine gives rise in different men to very different amounts of quinine in the blood.

10. The excretion-period of quinine by the urine differs greatly in different men—ranging from forty-one hours (after a single dose by mouth) to seven and a half days (after the last of a succession of large doses).

11. About 90 per cent. of the quinine injected intravenously disappears from the blood within one minute.

12. There is a striking association between symptoms of quinine intoxication and high concentrations of quinine in the blood.

13. When quinine is administered in a succession of large doses, an abnormally large proportion (from 90 to 93 per cent. of that ingested) is metabolised.

14. Quinine may fail to effect a radical cure of malaria even when it has reached, and maintained for some time, a concentration in the blood so high as to be barely tolerable to the patient.

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# A MENSURATIVE STUDY OF THE CYSTS OF *ENTAMOEBÆ COLI*

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## INTRODUCTION

Several workers have recently drawn attention to the variation in size of the cysts produced by two of the common intestinal entamoebae of man—*E. histolytica* and *E. coli*. Wenyon and O'Connor (1917), in their exhaustive investigations into problems relating to amoebic dysentery, have dealt with this subject, making particular reference to the cysts of *E. histolytica*, and Dobell and Jepps (1918), after a detailed study of the cysts of this organism, have concluded that it is really a collective species comprising a number of distinct races or strains, which can be distinguished from one another by the size of their cysts. It is natural to suppose that *Entamoeba coli* is also a collective species. Wenyon and O'Connor state (1917, p. 69): 'It is very probable that strains of *E. coli* exist as we have described for *E. histolytica*, one strain differing from another in the average size of its cysts. We have not, however, made any definite measurements to decide this point.' The suggestion that at least two strains occur has been made recently by Smith (1918). Since it was considered worth while to produce further evidence bearing upon the question, the measurement of a large number of *E. coli* cysts was undertaken, and in the following pages the results of this work are briefly recorded.

## MATERIAL USED AND METHODS EMPLOYED IN MAKING THE MEASUREMENTS

Cysts were measured from the stools of twenty-seven cases, who, so far as is known, became infected in different geographical regions. Of the twenty-seven cases studied, it may be mentioned that eleven (Cases 1, 2, 9, 10, 15, 18, 19, 20, 23, 26 and 27) had never been out

of England. The others were soldiers returned from various fronts. The stools from which the cysts were obtained were formed or semi-formed. In such material the great majority of *E. coli* cysts (nearly 90 per cent., as shown by Smith (1918)) are fully developed, i.e. eight-nucleate.

Cysts were measured either in saline or in Weigert's iodine solution, the latter being used if the material contained *E. histolytica* cysts as well as those of *E. coli*. It has been shown by Dobell and Jepps (1918) that iodine has no effect upon the size of the cysts of the former species, and there is no reason to suppose that cysts of *E. coli* are dissimilar in this respect. No further consideration, therefore, need be given to the question as to whether the average size of a series of measurements was obtained from cysts examined in iodine or in saline.

All measurements were made with a No. 3 ocular carrying a finely-ruled micrometer scale, in combination with a 1/12 in. oil immersion objective. The size of each cyst was recorded as the diameter in the case of spherical cysts, and as the mean of the major and minor axes in the case of elliptically-shaped cysts. The microscope was always adjusted so that one division of the micrometer scale represented  $0\cdot75\mu$ . It was not considered possible to estimate any measurement nearer than one division, i.e., the micrometer scale division was the actual unit of measurement employed. It is obvious, therefore, that a considerable error must enter into individual measurements, and in consequence it was decided to measure a large number of cysts from at least those infections that were being studied in detail so that the error might be as far as possible eliminated.\* In two cases over one thousand cysts have been measured, but the measurement of so large a number, or even of five hundred, from more than a few cases is no inconsiderable task, and in scanty infections it becomes impossible. In some instances only one hundred cysts were measured, and at the outset it seemed desirable to ascertain what value could be attached to the average size obtained from so small a series. This point, therefore, will now be considered.

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\* Since the division of the micrometer scale was the unit of measurement employed, a cyst recorded as measuring 20 divisions may equally well be any value between 19·5 and 20·5 divisions, i.e. the actual size of the cyst lies between  $14\cdot65$  and  $15\cdot35\mu$ .

# VALUE OF AN AVERAGE OBTAINED FROM MEASUREMENT OF ONE HUNDRED CYSTS

For the purpose of this preliminary investigation, one thousand cysts were measured from a stool passed by Case 3, and five hundred from a stool passed by Case 22. In the former instance ten cover-slip preparations were made, and one hundred cysts measured from each, while in the latter, one hundred cysts were measured from each of five cover-slip preparations. The results are set forth in Table I.

TABLE I.

Case	Preparation	Number of cysts measured	Range in size in $\mu$	Size of greatest frequency in $\mu$	Average diameter in $\mu$
3	1	100	12.75 - 21.0	15.0	15.44
	2	100	12.0 - 19.5	15.0	15.34
	3	100	12.0 - 20.25	15.0	15.33
	4	100	11.25 - 18.75	15.0	15.10
	5	100	12.75 - 21.0	15.0	15.45
	6	100	12.75 - 19.5	15.0	15.19
	7	100	12.75 - 19.5	15.0	15.38
	8	100	12.0 - 19.5	15.0	15.13
	9	100	11.25 - 19.5	15.0	15.31
	10	100	12.75 - 18.75	15.0	15.35
	Total	1000	11.25 - 21.0	15.0	15.30
22	1	100	15.0 - 23.25	18.75	18.53
	2	100	15.0 - 21.75	18.75	18.43
	3	100	14.25 - 22.5	18.75	18.74
	4	100	14.25 - 24.0	18.75	18.67
	5	100	15.0 - 24.0	18.0 and 18.75 equal	18.88
	Total	500	14.25 - 24.0	18.75	18.65

Inspection of Table I shows several points of interest. It seems clear that the two cases were infected with *E. coli* producing cysts

of different sizes, but this point will be dealt with later. The facts are presented in their present form to show the differences in the mean sizes obtained from the measurement of successive samples of one hundred cysts taken at random from the same stool. In Case 3 the averages vary from  $15.10\mu$  to  $15.45\mu$ , while in Case 22 they vary from  $18.43\mu$  to  $18.88\mu$ . In each instance the difference between the lowest and the highest average is approximately  $0.4\mu$ . We may conclude, then, that the mean size of cyst obtained from the measurement of one hundred is liable to an error of  $0.4\mu$ , and generally it will be less than this. For practical purposes it may be contended that this error is insignificant, but it is not altogether negligible in any detailed work relating to size-strains in minute organisms, and the advantage of having some idea of its magnitude will become evident later. The average size of the total number of cysts (one thousand) measured from one stool of Case 3 was  $15.30\mu$ . For the first five hundred the average was  $15.33\mu$ , while the second gave an average of  $15.27\mu$ . It seems, therefore, that a reliable average can be obtained from the measurement of five hundred cysts.

#### DETAILS OF MEASUREMENTS FROM TWENTY-SEVEN CASES

Details relating to the dimensions of cysts measured from twenty-seven different cases are given in Table II. Although the mean sizes have been obtained from the measurement of different numbers of cysts, it is convenient to arrange them in ascending order of size.

It will be seen from Table II that the average size of cyst varies in the cases studied from  $15\mu$  to  $19.5\mu$ , and that an almost regular gradation in size occurs between these two extremes. From this it might be concluded that there is little evidence for the existence of size-strains within the species. But if we consider the sizes of greatest frequency instead of average sizes, it becomes not impossible to regard the cases as falling into four fairly well-defined groups. These groups have been indicated in the Table. Group I includes Cases 1 to 8, in which the size of greatest frequency is always  $15\mu$  with a range from  $11.25\mu$  to  $21.75\mu$ . There seems little reason to doubt that these eight cases were infected with the same strain of *E. coli*—a strain producing cysts whose commonest size is  $15\mu$ , and whose average size is a little over  $15\mu$ . Case 3 is regarded as



TABLE II.

No. of Case	Number of cysts measured	Range in size in $\mu$	Size of greatest frequency in $\mu$	Average diameter in $\mu$
Group I	1	12'0 - 18'75	15'0	15'0
	2	12'0 - 18'75	15'0	15'0
	3	11'25 - 21'0	15'0	15'3
	4	12'0 - 21'0	15'0	15'3
	5	12'75 - 19'5	15'0	15'3
	6	12'0 - 21'75	15'0	15'6
	7	12'0 - 18'75	15'0	15'7
	8	12'75 - 21'0	15'0	15'8
Group II	9	11'25 - 21'0	15'0 and 18'0	16'1
	10	12'75 - 21'0	15'0 „ 16'5	16'1
	11	12'75 - 23'25	16'5 „ 18'75	16'6
	12	13'5 - 21'75	16'5 „ 18'0	16'6
	13	12'75 - 22'5	15'75 „ 18'75	16'8
	14	13'5 - 26'25	15'75 „ 18'75	17'2
	15	13'5 - 21'75	18'0	17'6
	16	13'5 - 27'75	16'5 and 18'75	17'7
Group III	17	14'25 - 22'5	18'75	18'3
	18	14'25 - 24'0	18'0	18'3
	19	14'25 - 26'25	18'75	18'3
	20	15'0 - 23'25	18'75	18'4
	21	14'25 - 24'0	18'75	18'5
	22	14'25 - 25'5	18'75	18'5
	23	14'25 - 23'25	18'75	18'6
	24	14'25 - 26'25	18'75	18'7
Group IV	25	15'75 - 25'5	18'75	18'7
	26	15'75 - 24'0	18'75	18'9
	27	14'25 - 27'75	18'75 and 21'75	19'5

representative of the group, and the mean size of cyst ( $15.3\mu$ ) may be taken as reliable since one thousand four hundred cysts were measured. The variations which occur in the average size of cyst for the remaining cases of the group are probably not significant, especially when we bear in mind the correction factor for an average obtained from only one hundred measurements.

Passing now to Group III (Cases 17 to 26), it will be found that the cysts measured from these cases range from  $14.25\mu$  to  $26.25\mu$ , the greatest frequency (with the exception of Case 18) occurring at  $18.75\mu$ . Here, again, it seems probable that the ten cases of Group III were infected with the same strain of *E. coli*—in this instance, however, a strain producing cysts whose size of greatest frequency is  $18.75\mu$ , and whose average size is somewhat below this. The average ( $18.5\mu$ ) obtained for one thousand three hundred cysts measured from Case 22 may be regarded as reliable, and the mean sizes obtained for the other cases in this group arrange themselves fairly closely round this value. The results so far considered, then, point to the existence of at least two strains of *E. coli*, and the evidence for this may be presented more fully by giving the actual measurements for the two cases studied in detail, viz., Cases 3 and 22. The distribution according to size of one thousand cysts from each of these cases is shown by the following figures:—

Dimensions of cysts in microns.

	11.25	12.0	12.75	13.5	14.25	15.0	15.75	16.5	17.25	18.0	18.75
Case 3 ...	2	5	12	110	169	283	180	122	69	27	11
Case 22 ...	...	...	...	...	4	16	33	78	136	192	248

	19.5	20.25	21.0	21.75	22.5	23.25	24.0	Average size
Case 3 ...	6	2	2	...	...	...	...	$15.3\mu$
Case 22 ...	123	73	48	33	10	3	3	$18.5\mu$

These figures show clearly the differences in the dimensions of the cysts in the two strains—differences which are perhaps better shown by plotting the figures in curves (fig. 1). The two curves are of the same form, unimodal and approximately symmetrical.

There is no clear indication in either case of the cyst population having been mixed, and it is considered as established that these two curves represent two single or pure strains of *E. coli*, distinguishable as follows by the size of the cysts they produce:—

- (1) Cysts of greatest frequency,  $15\mu$ ; average size,  $15.3\mu$ .
- (2) Cysts of greatest frequency,  $18.75\mu$ ; average size,  $18.5\mu$ .

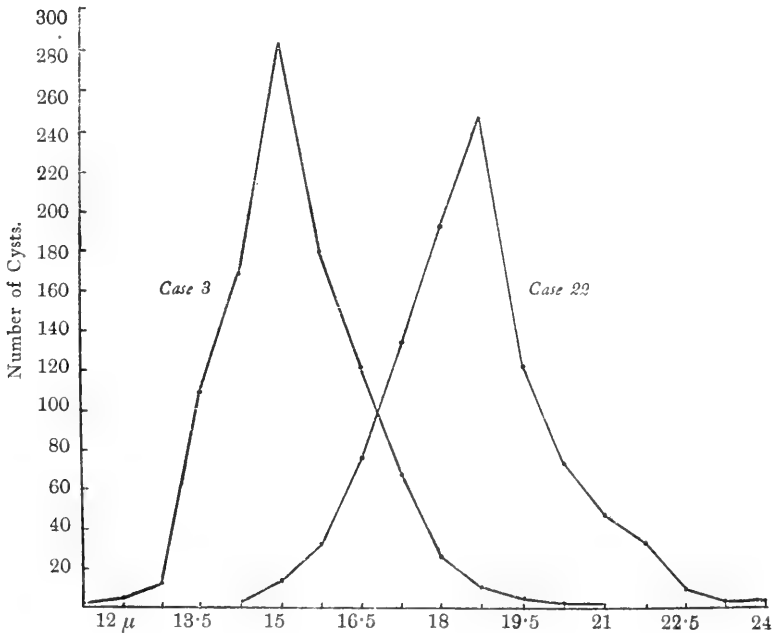


FIG. 1.

We may now consider the cases assigned to Groups II and IV of Table II. The average size of the cysts for the cases in Group II varies between  $16.1\mu$  for Case 9 and  $17.7\mu$  for Case 16. If we assume that a size-strain of *E. coli* exists between those just described, the average size of its cysts would approximate  $17\mu$ . An approximation to this has been obtained for Cases 13 and 14, where the average sizes are  $16.8\mu$  and  $17.2\mu$  respectively. The figures obtained for the measurements of the two hundred cysts from

Case 13 are as follows, and they are presented graphically in fig. 2:—

Dimensions of cysts in microns.

	12'75	13'5	14'25	15'0	15'75	16'5	17'25	18'0	18'75	19'5	20'25	21'0	21'75	22'5	Av. size
Case 13 ...	1	5	12	31	37	24	23	20	26	10	6	3	1	1	16'8 $\mu$

The feature of the curve is the presence of two apices; it is not unimodal as are the curves shown in fig. 1. The suggestion at once

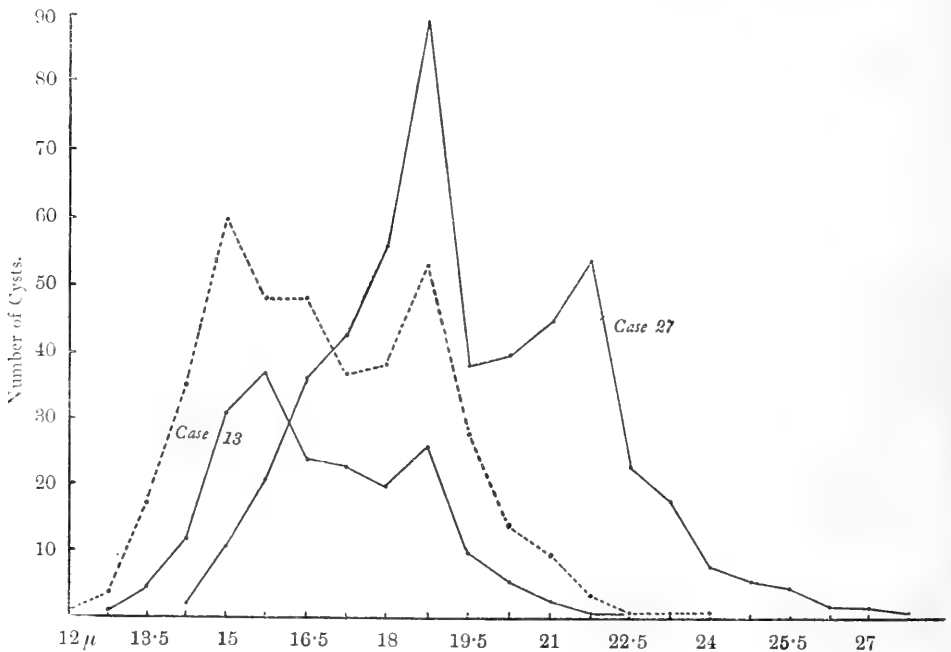


FIG. 2.

occurs that the curve for Case 13 may represent a mixed cyst population—that in this case the infection consisted of two strains co-existing in the same patient. Indeed, it seems probable that this case was infected with the two size-strains already defined. Whether this is the correct interpretation of the curve or not is very difficult to decide, and unfortunately the number of cysts measured is rather

small, but the following consideration lends some support to the idea. The dotted curve in fig. 2 represents the figures obtained by adding together the first two hundred cysts measured from Cases 3 and 22 respectively. The composition of this dotted curve is therefore known. The measurements it represents are those of two hundred cysts of the  $15\mu$  strain and two hundred of the  $18.75\mu$  strain. It will be seen that the curve so obtained is bimodal, and it is believed that the curve for Case 13 represents a similar condition, namely, a mixed cyst population. Possibly all the cases of Group II (Table II) may be explained in this way, for, with one exception, the frequency curves show two apices. It has to be noted, however, that the two apices are not at the same value in all the cases, and it is not clear that the variations may be due to different proportions of cysts belonging to the  $15\mu$  and  $18.75\mu$  strains existing in the same patient. Cases 10, 11, 12 and 16 suggest that a strain may exist producing cysts whose size of greatest frequency is  $16.5\mu$ , but in the absence of a pure infection with such a strain, its existence must for the present be left undecided.

Case 27, which is placed by itself in Group IV of Table II, must be considered separately. The first inspection of the cysts from the stool of this case at once showed that here was an infection containing many cysts obviously much larger than one generally finds in *E. coli* infections. Consequently, five hundred cysts were measured, their distribution according to size being shown by the following figures:—

Dimensions of cysts in microns.

	14.25	15.0	15.75	16.5	17.25	18.0	18.75	19.5	20.25	21.0
Case 27 ... ..	2	11	21	36	43	56	80	38	40	45

	21.75	22.5	23.25	24.0	24.75	25.5	26.25	27.0	27.75
Case 27 ...	54	23	18	8	6	5	2	2	1

The curve representing these figures is shown in fig. 2. It is bimodal with one mode at  $18.75\mu$ , which seems to indicate without much doubt the presence of cysts of the strain corresponding to this size. But the curve possesses a secondary, yet distinct apex at

$21.75\mu$ , which can scarcely be explained unless on the theory that a strain of *E. coli* exists producing cysts whose size of greatest frequency is  $21.75\mu$ . Unfortunately a pure infection with cysts of this strain has not been found during this investigation, and the average size of cyst has therefore not been obtained. Judging from the second portion of the curve for Case 27, however, the average diameter would probably be a little under  $21.75\mu$ .

Bringing together the results of the present work, then, we have some evidence for believing that *E. coli* is a collective species comprising at least three strains or races which can be distinguished by the size of their cysts. The approximate dimensions of the cysts in each of these three strains are as follows:—

1. Cysts of greatest frequency,  $15\mu$ ; average diameter,  $15.3\mu$ .\*
2. " " "  $18.7\mu$ ; " "  $18.5\mu$ .
3. " " "  $21.7\mu$ ; " " (?)  $21.5\mu$ .

A cyst from each of these strains is shown in fig. 3, the commonest size of each having been selected for the purpose of illustrating the different races.

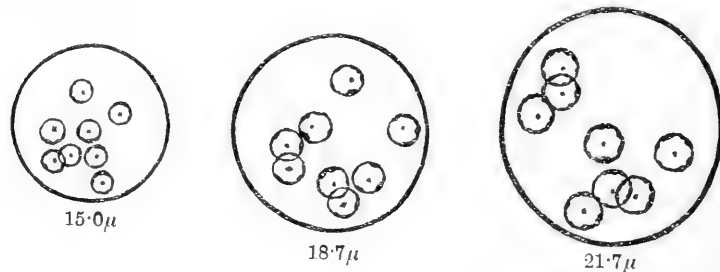


FIG. 3. A cyst of each of the three size-strains described in the text. Drawn to the same scale, under  $1/12$  in. oil immersion and No. 8 ocular, with the aid of a camera lucida.

While only three size-strains or races of *E. coli* have here been recognised, it is not to be concluded that this is the actual number which exists. Had it been possible to study fully a greater number of infections, it is probable that other strains would have been discovered. Wenyon and O'Connor, although they do not give any definite measurements, state 'We have frequently seen infections in which practically all the cysts were over 20 microns, while once the

\* If a more accurate method of measuring had been employed, it is probable that the average size would have coincided with the size of greatest frequency. The mean size obtained ( $15.3\mu$ ) actually lies in the same modal group of measurements ( $14.65$ – $15.35\mu$ ) as the size of greatest frequency.

average size was well over  $25\mu$ . This statement obviously refers to strains producing large cysts, and the first mentioned might correspond to the  $21.7\mu$  strain which I have described. The strain which produces cysts averaging about  $25\mu$  must be exceedingly rare.

But whatever the actual number of races, it is obviously important for the final proof of their existence to show that they remain constant in size. To do this it is necessary to measure cysts from the same case at intervals over a considerable period of time, and in this connection it is useful to know what value may be attached to the mean size obtained from the measurement of, say, one hundred cysts. It is not always possible to measure large numbers. We have already seen that the average size of one hundred measurements is liable to an error of approximately  $0.4\mu$ . With this in mind, we may consider the results presented in Table III, which shows the average size of cysts obtained from the measurement of various samples from Cases 3 and 22 on different dates.

TABLE III.

Case	Date of examination	Number of cysts measured	Size of greatest frequency in $\mu$	Average diameter of cyst in $\mu$
3	19.3.18	100	15.0	15.32
	23.3.18	100	15.0	15.17
	26.3.18	100	15.0	14.98
	5.4.18	1000	15.0	15.30
	24.4.18	100	15.0	15.02
22	27.5.18	500	18.75	18.40
	15.6.18	500	18.75	18.65
	18.6.18	100	18.75	18.65
	9.7.18	100	18.75	18.74
	12.7.18	100	18.75	18.41

For Case 3 no significant change in size occurred during the five weeks when observations were made. For Case 22 when, on two occasions, five hundred cysts were measured at an interval of nearly three weeks, the difference of  $0.25\mu$  in the mean size is perhaps a

little greater than might have been expected from so large a sample. In the interval between the two observations the patient had received treatment with emetine bismuth iodide for a concurrent infection of *E. histolytica*. It is not impossible that the slight increase in size of the *E. coli* cysts which re-appeared after treatment is in some way connected with the administration of the drug. Dobell and Jepps have drawn attention to the larger size of cysts of *E. histolytica* which first appear in a relapse after treatment, and Smith has recorded a similar phenomenon for *E. coli* cysts. It appears, therefore, from the results set forth in Table III that, if any change in mean size of cyst does occur from day to day, it is comparatively small, and there seems little doubt that if a case be infected with a *pure* strain producing cysts averaging about  $15\mu$  then that case will continue to pass cysts having that average size. Similarly, an infection with a *pure* strain producing cysts about  $18.5\mu$  will remain constant. We should not expect, for instance, that the one would suddenly change into the other. It is obvious, of course, that if a case be infected with two strains the number of cysts passed from day to day belonging to the different strains may vary, and there may be consequently a considerable daily variation in the mean size of cyst. As already pointed out, it is considered possible to regard all the cases comprising Group II of Table II as having double infections, i.e. they were infected with two size-strains of *E. coli*. Unfortunately, only in two cases were cysts measured on different days. The first hundred cysts measured from Case 11 averaged  $16.4\mu$ , while from a stool passed three days later the average of one hundred was  $16.9\mu$ . In the second instance, Case 13, the average obtained from the first measurement of one hundred cysts was  $16.5\mu$ , and a fortnight later a second series of one hundred gave  $17.1\mu$  as the average diameter. These differences are not outstanding, although they exceed the error likely to be obtained through using a small sample, and it is suggested that they may lend further support to the theory already advanced that each of the Cases 9 to 16 had a double infection, and constancy in the mean size of cysts passed from day to day would not therefore be likely to occur.

Frequency curves for the size of *E. coli* cysts have been given by various workers. Kuenen and Swellengrebel (1913) give a curve which shows two apices—one at  $18\mu$  and another at  $20\mu$ —with a dip at  $19\mu$ . Since the curve is based on only one hundred cysts, it is



difficult to draw any conclusions from it, but if smoothed out, it might be interpreted as representing a strain corresponding fairly closely to the  $18.7\mu$  strain which I have described.

A frequency curve given by Mathis and Mercier (1917) shows three well-defined apices corresponding to cysts measuring (in the fresh state)  $16.5\mu$ ,  $18\mu$  and  $19.5\mu$ . The remarkable feature of their curve, however, is the fact that only three or four cysts exist between these sizes—a feature which I cannot understand since the apices in the curve fall so closely together. Even if it be admitted that strains occur of the sizes given by these authors, it would be necessary, in order to explain their curve, to assume that each strain showed practically no range in the size of its cysts. Unfortunately, Mathis and Mercier are satisfied with a curve which represents one hundred measurements, and it is difficult to estimate how far their results would have been modified if they had measured a much larger number of cysts.

The general curve for one thousand cysts measured from a large number of cases by Smith (1918) shows a single apex at  $16.7\mu$ , while the average size is  $17.3\mu$ . But the results shown in Table VIII of his paper suggest that his infections '9', '10' and '11' correspond to the  $18.7\mu$  strain, while his infections '1' and '2' are probably the same as the  $15\mu$  strain. A general curve for two thousand seven hundred cysts measured during the present work is shown in fig. 4. This number has been obtained by adding together the first hundred cysts measured from each of the twenty-seven cases studied, so the contribution of each case to the total number is equal. The curve represents the following figures:—

Dimensions of cysts in microns.

11.25	12.0	12.75	13.5	14.25	15.0	15.75	16.5	17.25	18.0	18.75	19.5
1	8	24	90	183	382	305	301	287	330	353	170

20.25	21.0	21.75	22.5	23.25	24.0	24.75	25.5	26.25	27.0	27.75
90	82	36	18	12	6	2	3	5	2	1

The curve is bimodal, with modes at  $15\mu$  and  $18.75\mu$ , corresponding to the two races producing cysts of these respective sizes. The one hundred cysts contributed by Case 27 are insufficient to indicate in the general curve the  $21.75\mu$  strain found in that case.

The average diameter of the two thousand seven hundred cysts is  $17.1\mu$ , which is almost identical with that obtained by Smith for one thousand cysts. His results and mine are, therefore, not

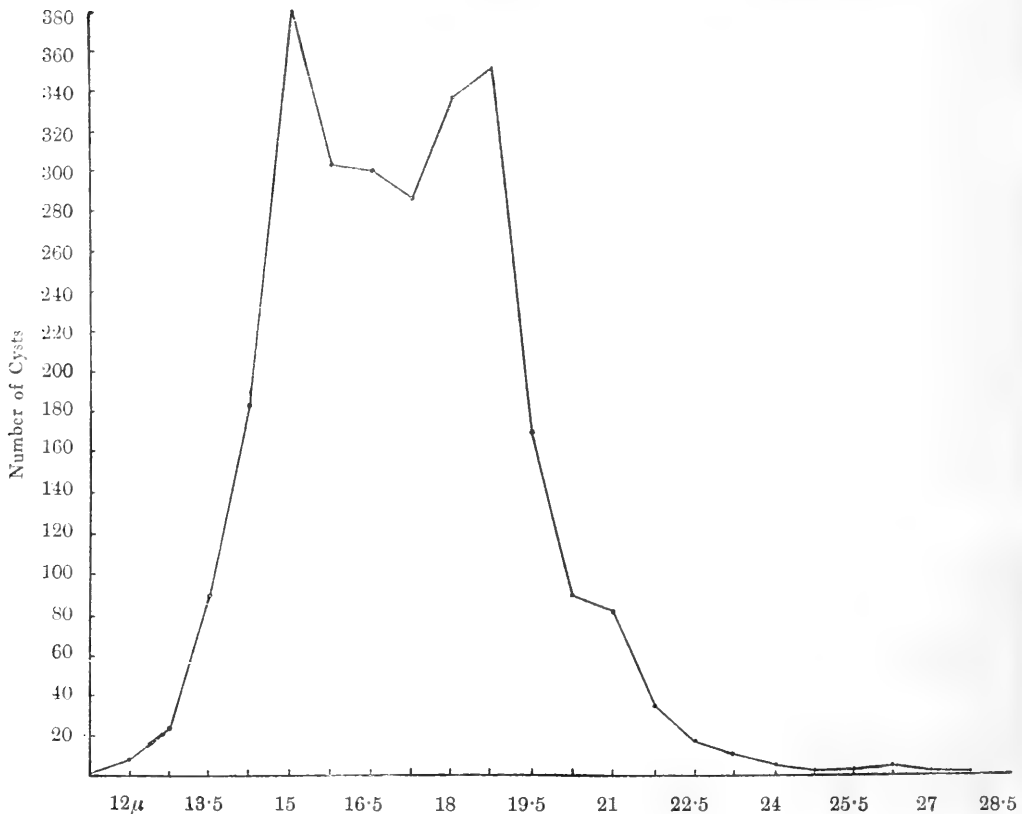


FIG. 4.

incompatible, and a general curve for the size of *E. coli* cysts may vary to some extent according to the number of cases studied, the number of strains encountered, and the number of cysts contributed by each case.

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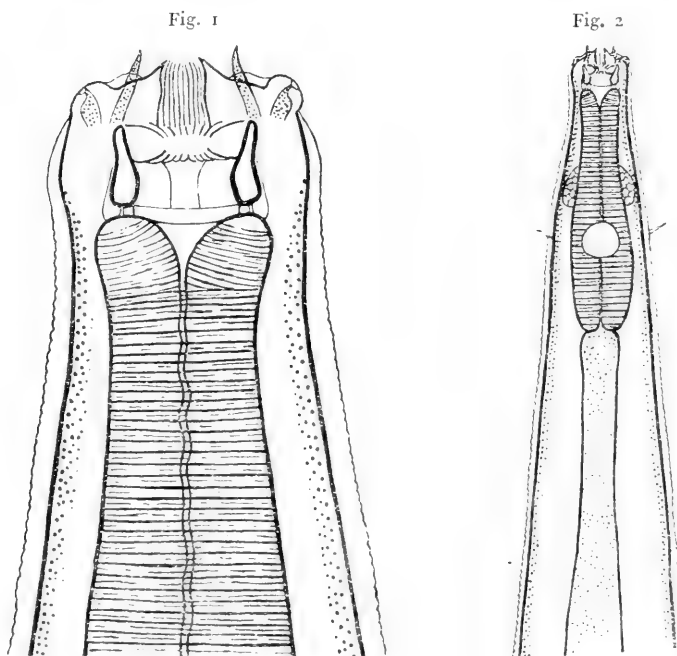
# STRONGYLIDÆ IN HORSES

## VI. *CYLCOSTOMUM PSEUDO-CATINATUM* sp. n.

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SIZE AND SHAPE. A small delicate species of the GENUS *Cylicostomum*, the female being slightly larger than the male. Ten males and ten females were measured. The males were from 5·2 to 6·6 mm., average 5·8 mm.; the females front 6·1 to 7·7 mm., average 6·7 mm.: the greatest breadth, in those worms which were properly orientated, averaged, males 260 $\mu$ , females 320 $\mu$ .



FIGS. 1-2. *Cylicostomum pseudo-catinatum* sp. n.

Anterior extremity, ventral view; Fig. 1  $\times$  360. Fig. 2  $\times$  90.

HEAD. The neck separating the head from the body is distinct.

*Mouth collar.* Marked off from the rest of the skin by a definite constriction.

*Head papillae.* Sub-median, pointed and projecting beyond the elements of the external leaf crown, their extremities are not separated off by lateral notches; lateral, prominent.

*Mouth capsule.* Ellipsoidal in transverse section, the ratio of the lateral diameter to the dorso-ventral diameter of the anterior opening

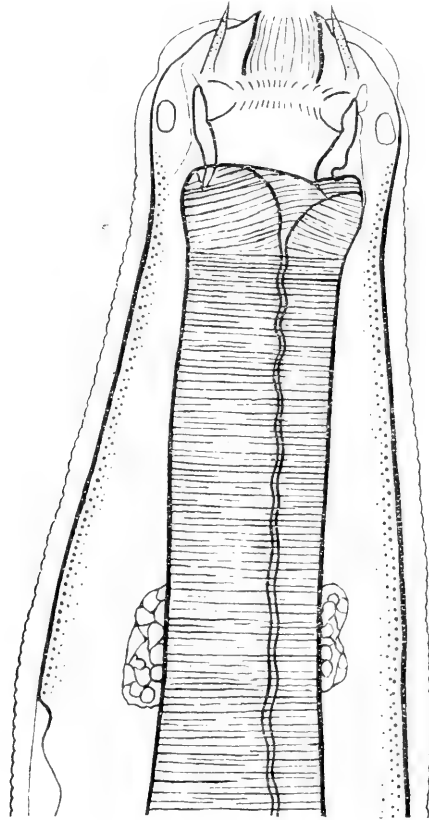


FIG. 3. *Cyclostomum pseudo-catinatum* sp. n.

Anterior extremity, lateral view,  $\times 360$ .

of the buccal capsule being about 1 to 1.2. When the worm is properly orientated the walls of the mouth capsule seen in optical section are slightly kneed inwards, are very stout posteriorly and slender anteriorly (fig. 1). When viewed laterally the walls of the buccal capsule converge considerably from before backwards and the ventral wall is distinctly larger than the dorsal owing to the floor of the buccal capsule being set obliquely, so that the cavity is deeper ventrally than dorsally (fig. 3). The antero-posterior diameter (i.e. the distance from the anterior to the posterior opening) of the buccal

capsule varies in the males from  $22.5\mu$  to  $25\mu$ , average  $24\mu$ , and in the females from  $24\mu$  to  $29\mu$ , average  $27\mu$ . In the males the lateral diameter of the buccal capsule at the anterior opening varies from  $34\mu$  to  $38\mu$ , average  $36\mu$ , and at the posterior opening from  $31.5\mu$  to  $33.5\mu$ , average  $33\mu$ ; in the females the lateral diameter of the buccal capsule at the anterior opening varies from  $41\mu$  to  $47.5\mu$ , average  $43\mu$ , and at the posterior opening from  $34.5\mu$  to  $37\mu$ , average  $36\mu$ . The ratio of the lateral diameter of the anterior opening of the buccal capsule to that of the posterior opening is therefore in the male 1.1 to 1, and in the female 1.2 to 1. The ratio of the lateral diameter of the buccal capsule at the anterior opening to the antero-posterior diameter is in the male 1.5 to 1, and in the female 1.6 to 1.

*Dorsal oesophageal gutter.* Does not project into the buccal capsule.

*Leaf crowns.* The external leaf crown consists of twenty large pointed elements arising from the mouth collar. The internal leaf crown consists of numerous long narrow elements arising from the middle of the mouth capsule just anterior to the knee, but not within a single plane, the line of origin laterally being somewhat nearer the anterior opening of the mouth capsule than it is dorsally and ventrally.

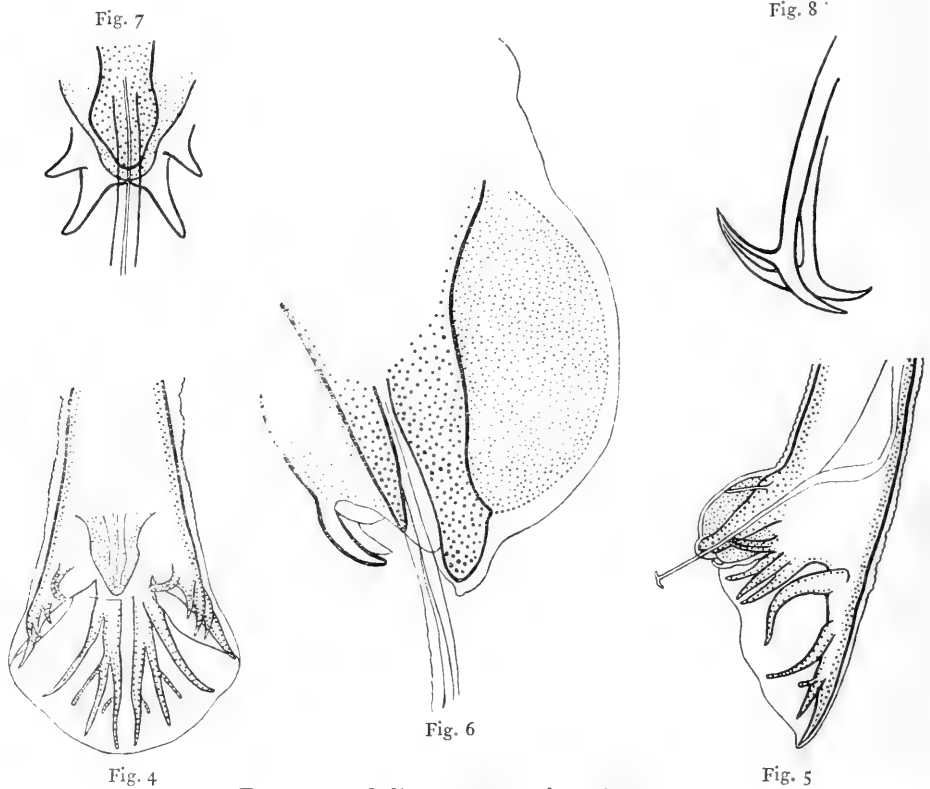
**OESOPHAGUS.** The length in eight males varied from  $314\mu$  to  $349\mu$ , average  $330\mu$ , and the greatest breadth from  $70\mu$  to  $82\mu$ , average  $74\mu$ ; the ratio of breadth to length is 1 to 4.4. In eight females the length ranged from  $322\mu$  to  $363\mu$ , average  $347\mu$ , and the greatest breadth from  $72\mu$  to  $83\mu$ , average  $79\mu$ ; the ratio of breadth to length is 1 to 4.4. The ratio of the length of the oesophagus to that of the worm is 1 to 19.

**EXCRETORY BLADDER.** Lies over the 3rd or 4th fifth of the oesophagus behind the nerve ring. The distance of its posterior margin from the posterior end of the oesophagus varies considerably, e.g., in sixteen worms from  $67\mu$  to  $152\mu$ , average  $108\mu$ .

**CERVICAL PAPILLAE.** Lie about the same level as the excretory bladder.

**POSTERIOR EXTREMITY OF MALE.** The dorsal lobe of the bursa is short, almost semicircular. The main trunk of the posterior ray and the second lateral branch are as a rule each furnished with a small accessory branch on the external side (fig. 4). In ten worms the

length of the main trunk of the posterior ray from the tip to the point of origin of the postero-external rays varied from  $230\mu$  to  $298\mu$ , average  $259\mu$ . The ratio of the average length of the main trunk of the posterior ray to the average length of the male worm is 1 to 22.4.



FIGS. 4-8. *Cylicostomum pseudo-catinatum* sp. n.

Fig. 4: Posterior extremity of male, ventral view,  $\times 90$ . Fig. 5: Posterior extremity of male, lateral view,  $\times 90$ . Fig. 6: Genital cone and appendages, lateral view,  $\times 360$ . Fig. 7: Genital appendages, ventral view,  $\times 360$ . Fig. 8: End of spicules,  $\times 1360$ .

*Genital cone.* The dermal collar is well developed on both the ventral and dorsal surfaces of the genital cone. The genital appendages on each side are represented by slight elevations furnished with two conical processes, the inner being the larger (figs. 6 and 7).

*Spicules.* The ends of the spicules are barbed as shown in fig. 8.

**POSTERIOR EXTREMITY OF FEMALE.** The end of the body is bent dorsally at right angles. The ventral prominence is large and projecting. The tail is very short and conical (fig. 9.). In six worms the distance between the anus and vulva varied from  $45\mu$  to  $85\mu$ , average  $61\mu$ ; and the distance measured straight along the middle line of the tail from the tip to a line drawn horizontally through the anus varied from  $54\mu$  to  $81\mu$ , average  $69\mu$ .

**DIAGNOSIS.** The following are the chief diagnostic characters of this worm:—

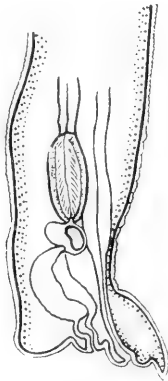


FIG. 9. *Cylicostomum pseudo-catinatum* sp. n

Posterior extremity of female, lateral view,  $\times 90$ .

1. Size, small: average length, males 5.8 mm. and females 6.7 mm.

2. Buccal capsule: anterior opening ellipsoidal, ratio of lateral to dorso-ventral diameter of anterior opening of capsule is 1 to 1.2; walls when seen in optical section, in properly orientated worms, slightly kneed, very thick posteriorly and slender anteriorly; ratio of breadth at anterior opening to antero-posterior diameter 1.5 to 1.

3. Dorsal oesophageal gutter does not project into buccal capsule.

4. Dorsal lobe of bursa short, almost semicircular; ratio of length of posterior ray to total length of male worm 1 to 22.4. The genital appendages are slight elevations furnished with two conical processes.

5. Termination of female body bent dorsally at right angles; ventral prominence large and projecting; tail short and conical.

This species clearly belongs to the *catinatum-alveatum* group of Cylicostomes. It most closely resembles *C. catinatum*, but may be distinguished from this worm by its small size and by the character of the genital appendages. We propose for this species the name *Cylicostomum pseudo-catinatum*.



# QUELQUES REMARQUES CONCERNANT LES MOEURS DE LA *GLOSSINA TABANIFORMIS*, WESTW.

PAR

LE DR. J. SCHWETZ

*(Received for publication August, 1918)*

La *Glossina tabaniformis*, Westw., est une des espèces de glossines les plus rares et les moins étudiées. Les quelques rares spécimens connus proviennent de l'Afrique Occidentale. Au Congo Belge, la *G. tabaniformis* a été trouvée, à Léopoldville, mais, autant que je sache, elle n'a pas été signalée ailleurs.

Je crois par conséquent intéressant de signaler la découverte de la *G. tabaniformis* dans le nord de la province du Katanga. Cette trouvaille est d'autant plus intéressante que les grandes espèces de glossines, la *G. fusca* et la *G. brevipalpis*, ne dépassent pas, dans cette région, à l'ouest, le bassin de la rivière Lomami. Pendant plusieurs années de voyages et de recherches je n'ai jamais trouvé un seul spécimen de *G. brevipalpis* ni de *G. fusca* dans le bassin de la rivière Sankuru, grand affluent du fleuve Congo.

Mais le 19 février 1917, en allant de Tsofa à Pania Mutombo, c'est à dire du Lomami au Sankuru, j'ai capturé une grande glossine au passage du petit ruisseau clair *Buitshi*, affluent de la rivière Lubefu, affluent du Sankuru. C'était à 8 a.m. et la mouche en question se trouvait sur un tronc d'arbre, posée avec la tête en bas, comme c'est l'habitude des grandes espèces de glossines. Au premier coup d'oeil la mouche me semblait être une *G. fusca*, ce qui était déjà peu ordinaire pour la région en question; mais un examen ultérieur plus attentif me démontra qu'il s'agissait d'une espèce plus rare, et Monsieur le Professeur Newstead m'informa qu'il s'agissait d'une *G. tabaniformis*.

J'ai donc décidé de réexaminer le même endroit, la *Buitshi*, pour voir si la *G. tabaniformis* s'y trouvait en plus ou moins grand nombre, et pour éventuellement faire quelques observations sur ses moeurs. Ayant été empêché de me rendre sur place moi-même, j'y ai envoyé mon premier aide fly-boy qui travaille avec moi depuis plusieurs années et qui est aussi compétent dans la question que moi-même. Je lui ai adjoint quelques hommes et lui ai donné toutes

les instructions nécessaires. Mes hommes consacrèrent à l'examen de la *Buitshi* quatre jours (20-23 mars 1918) et m'en rapportèrent, outre un certain nombre de *G. palpalis*, deux *G. tabaniformis* (mâles, comme le premier spécimen).

Et voici les renseignements concernant ces deux mouches.

Le ruisseau *Buitshi* se trouve entre le 25 et le 24 long. E. et très légèrement au sud du 5 par. S., à peu près à mi-chemin entre Tshofa et Pania Mutombo et à environ 125 kilomètres au nord de Kabinda. C'est dans la petite chefferie de Butwele (Bamale), à quelques kilomètres à l'est de la rivière Lubefu. La *Buitshi* est un petit ruisseau clair. En amont et en aval du passage, où furent trouvées les trois glossines en question, le ruisseau coule dans une large galerie forestière, mais au passage lui-même cette bande forestière est étroite : une vingtaine de mètres.

Comme je l'ai déjà dit, plusieurs *G. palpalis* furent capturées dans le courant de la journée (pendant trois jours), mais aucune autre espèce de glossine n'a été aperçue *en activité* pendant tout ce temps : ni durant la journée (heures de l'activité de la *G. palpalis*), ni avant le coucher ni après le lever du soleil (moments de l'activité de la *G. brevipalpis*), ni tard dans la soirée, à 7-10 p.m. (heures de l'activité de la *G. fusca*). Seulement une *G. tabaniformis* a été trouvée un peu après le lever du soleil, posée sur un tronc d'arbre, à environ 150 mètre du sol, avec la tête en bas ; et une deuxième fut trouvée dans la même position le lendemain, au moment du coucher du soleil.

Plusieurs mètres carrés, dans plusieurs endroits, furent déboisés et examinés au point de vue des pupes, mais sans le moindre résultat.

Et c'est tout. Il est évident que vu le nombre si restreint de *G. tabaniformis* capturées (trois), il serait imprudent de se hasarder à en tirer des conclusions concernant ses moeurs. Il faut donc attendre un endroit et un moment plus propices. Je me bornerai à dire qu'il est peu probable que les quelques renseignements attribués aux moeurs de la *G. tabaniformis*, concernent en réalité cette espèce et non pas la *G. fusca* (voir E. Austen : 'A Handbook of the Tse-tse Flies,' 1911, p. 83). En effet, c'est la *G. fusca* qui pique, la nuit, jusqu'à 11 p.m. A moins que les moeurs de la *G. tabaniformis* et celles de la *G. fusca* soient identiques, ce qui reste à voir et à démontrer.

KABINDA, Avril 1918.

# QUELQUES OBSERVATIONS PRÉLIMINAIRES SUR LES MOEURS DE LA *PANGONIA ZONATA*, WALK.

PAR

LE DOCTEUR J. SCHWETZ

(*Mission d'Études au Congo-Belge*)

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Si les Tabanides en général (*Haematopota*, *Tabanus*, et même *Chrysops*) sont assez communes au Congo, surtout à proximité de l'eau, les *Pangonia* par contre sont bien rares, au moins dans la région (Nord Katanga) que j'étudie depuis plusieurs années. Pendant mes longs voyages dans le district du Lomami, les régions voisines, je n'en ai vu que de très rares spécimens. Parmi de très nombreuses tabanides capturées dans les environs de la station de Kabong, en mai 1913, je n'ai pas trouvé une seule pangonia.

Mais le 28 mai 1914, en partant du village Birikwiba à environ 50 kilomètres au Sud de la station de Kisengwa, je fus frappé, dès le matin, par le bruit sui-generis du vol de nombreux taons. Vers neuf heures du matin ce bruit est devenu presque constant; mais ce vol était si rapide que je ne pouvais rien voir. Plusieurs de mes porteurs ont quand même fini par capturer et m'apporter plusieurs de ces mouches: c'étaient des pangonia. Et dans le courant de la journée on m'en a ramassé une cinquantaine.

Le lendemain je me suis arrêté près du village Kakanu, à 25 kilomètres au Sud de Kisengwa, où je me suis installé près d'un petit village abandonné et entouré d'une large bande de forêt (galerie forestière de la rivière Kukwe). Les pangonia y étaient si nombreuses qu'en deux jours mes quarante porteurs en capturèrent exactement 1,300 spécimens.

M'étant arrêté à Kakanu pour faire des observations sur les glossines, je m'occupais en somme très peu des pangonia, et le troisième jour j'ai dû subitement partir pour Kisengwa, de sorte que, à cette époque, je n'ai fait aucune observation sérieuse sur notre mouche. Malgré que les pangonia grouillaient, pour ainsi dire autour de moi, je n'en ai pas été piqué une seule fois, pas plus que mon grand chien qui m'accompagnait. Deux ou trois porteurs m'ont vaguement dit qu'ils avaient été piqués par les pangonia, mais personnellement je ne l'ai pas constaté. J'ai gardé le souvenir que ces mouches s'arrêtaient sur les fleurs, mais même ce souvenir était assez vague. J'ajouterai que j'ai vu ces mêmes pangonia, jusqu'à Kisengwa, mais que, après cette station, ces mouches ont subitement disparu.

Toutes ces pangonia, qui se trouvent actuellement au British Museum (Natural History) et au Liverpool School of Tropical Medicine, appartiennent au moins à deux espèces différentes (et peut-être même trois) : *P. zonata*, Walk., et une ou deux espèces voisines (*P. oldii*, Aust. ?, *P. ruppelli*, Bezzi ?).

C'était, comme je viens de le dire, le 28-31 mai. Mais trois mois plus tard, le 23 août, quand je suis de nouveau revenu à Kakanu, je n'ai plus trouvé une seule pangonia, mais pas une seule !

Revenu dans la région, à Katombe, en 1916, j'ai immédiatement pensé à mes pangonia et j'ai envoyé à Kakanu quelques uns de mes hommes (les mêmes qui m'y avaient accompagné précédemment), mais ils en sont revenus sans une seule mouche. C'était en février. Au commencement avril, même résultat négatif. Mais vers le 15 de ce même mois, me trouvant au fleuve Lualaba, entre Kabalo et Kongolo, j'ai capturé une *P. zonata* en train de sucer le nectar d'une labiée. Au commencement juillet me trouvant à Kabinda, j'ai de nouveau envoyé mes aides chercher des pangonia à Kakanu, mais mes gens sont de nouveau revenus les mains vides.

Je dois dire que quand j'ai envoyé mes gens en février, ils me dirent d'avance qu'ils n'en trouveraient probablement *pas encore* les mouches en question et m'en donnèrent la raison suivante :

‘ Les pangonia du mois de mai à Kakanu, volent exclusivement autour et sur des fleurs de “ Nafimbia ” (c'est le nom indigène d'une boraginée aux fleurs bleues et aux bractées très piquantes). Ces plantes ne fleurissant que depuis la fin du mois d'avril jusqu'à la

fin du mois de juin, ce n'est que durant ces deux mois que l'on peut trouver les pangonia. Nous n'avons pu trouver ces mouches en août, parce que les fleurs de "Nafimbia" étaient déjà fanées; or, en février, ces mêmes fleurs n'étaient pas encore épanouies.'

J'ai, bien entendu, trouvé cette explication très intéressante, quoique nécessaire à vérifier, et j'ajouterai que le 'Nafimbia' \* est une plante annuelle très répandue partout et surtout à proximité des villages. A Kabinda, où je réside depuis plusieurs années, les 'Nafimbia' croissent en vraies plantations autour de la station, quoique je n'y aie jamais vu une seule pangonia, pas même en mai, quand ces mêmes champs resplendissent de leurs jolies fleurs bleues. J'ajouterai, enfin, que dans la région en question, 6ème P.S., la saison sèche dure, grossomodo, 5 mois : mai-septembre.

Malgré mon grand désir de revenir à Kakanu au mois de mai, je n'y suis pas parvenu, mais j'ai fini par y arriver le 1 juillet 1917. J'y ai encore trouvé des pangonia, mais en très petit nombre; en si petit nombre que mes vingt-cinq hommes n'en capturèrent en quatre jours (1-4 juillet) que 208 spécimens, dont :

1<sup>e</sup> *P. zonata* : 122 femelles et 56 mâles,

2<sup>e</sup> *P. sp. ?* : 28 femelles et 2 mâles.

Ce qui m'intéressait tout particulièrement, c'était de pouvoir me convaincre, de visu, si la *P. zonata* et l'espèce voisine étaient des hématophages ou non.

Le moment était évidemment peu propice pour faire ces observations; mais comme je n'étais pas sûr de pouvoir revenir à Kakanu en mai, j'ai essayé. Et je dirai de suite que mon but a été atteint : j'ai obtenu une réponse nette et catégorique à la question que je m'étais posée. Je vais donc exposer ici brièvement ce résultat, quitte à compléter ultérieurement mes observations, si un heureux hasard me ramène dans l'endroit en question au mois de mai.

Les indigènes du petit village Kakanu, à qui j'avais demandé des renseignements sur les pangonia, me répondirent d'abord spontanément que cette mouche apparaissait et disparaissait en même temps que les fleurs 'Nafimbia.' La réponse était moins catégorique et moins spontanée en ce qui concerne l'hématophagie de notre mouche. Les indigènes m'assuraient qu'ils n'avaient jamais

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\* *Blepharis* sp. [Ed.]

été piqués par les pangonia. Ces dernières 's'arrêteraient' quelquefois sur les chèvres et les moutons, mais sans les effrayer ni même déranger. Il n'existe pas de gros bétail dans la région. Quant au gibier (buffles et antilopes), qui y est, par contre, abondant, il est évident que les indigènes n'ont rien pu me dire à ce sujet. Sur deux buffles tués j'ai trouvé moi-même de nombreuses *Haematopota* et même une *G. palpalis*, mais pas une seule pangonia.

Je m'installe à côté de la petite rivière Kukwe, près d'une pelouse (ancienne plantation) entourée d'une large bande de forêt. La savane boisée d'au delà de la forêt est brûlée. La pelouse est aussi brûlée en partie, mais la végétation 'advéctice' (des abords des villages) habituelle—solanées, convulacées, cucurbitacées, labiées, et surtout malvacées—y est encore assez abondante. Le 'Nafimbia' y existe également, surtout près de la lisière de la forêt, mais ses fleurs sont déjà en grande partie desséchées.

*Première observation: 1<sup>er</sup> jour*

Les pangonia apparaissent vers 9 heures a.m. et disparaissent vers 5 p.m. En volant, elles font le même bruit que les autres grandes tabanides (*Tabanus*), mais leur vol est si rapide que l'on ne peut pas les apercevoir elles-mêmes. Quand elles voltigent sur une fleur, elles font le même bruit que les hyménoptères (abeilles guêpes); et, en même temps que les pangonia, les guêpes voltigent également sur les fleurs. La confusion est assez facile, d'autant plus que, de loin, les deux insectes se ressemblent légèrement.

Je vois fréquemment les pangonia s'arrêter sur diverses fleurs et même sur les feuilles de buissons, mais sans sucer leur nectar. Je vois, par contre, à plusieurs reprises nos mouches enfoncer leur trombe dans les fleurs de 'Nafimbia'. Vers midi les pangonia disparaissent presque complètement, mais réapparaissent vers 3 p.m.

Malgré que je me promène sur la pelouse avec une quinzaine d'hommes (très sommairement habillés) et mon chien, aucune pangonia n'essaye de nous piquer. Dans l'après-midi mes hommes m'apportent plusieurs pangonia capturées dans la forêt. J'autopsie plusieurs mouches et je ne trouve dans leur abdomen qu'une masse végétale verte, mais un homme m'apporte une mouche écrasée et tachetée de sang (une femelle).

*Deuxième observation : 2<sup>e</sup> jour*

Lors de mon premier passage par Kakanu, les pangonia furent capturées sur la pelouse et non pas dans la forêt. Mais comme cette fois-ci on m'apporte quelques unes des ces mouches de la forêt, j'y vais moi-même. Je pars à 9 a.m. A la lisière de la forêt je vois déjà quelques pangonia, mais dans la forêt elle-même je les trouve en beaucoup plus grand nombre que sur la pelouse, et entre 9 a.m. et midi, mes gens en capturent une cinquantaine (dont la moitié environ : mâles).

Serait-ce parce que la savane environnante était fraîchement brûlée, et que le seul refuge pour les pangonia restait par conséquent la forêt ? Ou serait-ce parce que même en 'temps normal', c'est-à-dire en mai, les pangonia habiteraient également la forêt ? C'est ce que je ne saurais pas dire pour le moment, n'ayant pas exploité précédemment la forêt à ce point de vue. Mais, d'autre part, il est un fait que même en pleine forêt je vois les pangonia diminuer vers 11 a.m., et vers midi je n'en vois presque plus. Il semblerait donc qu'aux pangonia il faut également une certaine fraîcheur, contrairement à ce que quelques auteurs ont dit à ce sujet.

En pleine forêt je n'ai pas trouvé de 'Nafimbia', mais les pangonia semblaient s'en passer sans grand inconvénient, en voltigeant sur et autour d'autres fleurs et notamment sur des labiées et sur de grandes fleurs blanches en grappes d'un buisson, plante vivace (que je n'ai pas su déterminer). Je vois également à plusieurs reprises les pangonia se poser sur des feuilles ordinaires.

A noter que j'ai vu à plusieurs reprises les pangonia 'planer' d'une manière remarquable. L'insecte se tient sur place, à un ou deux mètres du sol, ou sur un buisson, les ailes étalées, sans bouger ni faire le moindre bruit, mais en 'vibrant' légèrement, et cela pendant une ou deux minutes. Cette étrange attitude démontrerait que ces pangonia peuvent piquer au vol, c'est à dire sans s'appuyer sur leurs pattes, mais en planant. Mais piquent-elles ? Voilà la question.

Je vois à plusieurs reprises les pangonia se poser sur mes hommes, mais sans essayer de les piquer. Enfin, vers midi, un de mes aides m'apporte une pangonia capturée au moment qu'elle le piquait dans la jambe. Je constate effectivement à l'endroit indiqué de la pique

une gouttelette de sang; mais la mouche, une femelle, bien entendu, ne contient pas de sang; probablement parce qu'elle fut capturée avant d'avoir eu le temps de s'en gorger.

*Troisième observation: 3<sup>e</sup> jour*

Pour pouvoir enfin résoudre définitivement la question, je fais ceci: j'arrive près de la lisière de la forêt à un endroit où les pangonia volent en relativement grand nombre, et je m'arrête. Je dis aux dix hommes qui m'accompagnent de s'arrêter également et de ne pas bouger quoiqu'il arrive. Quelque temps après, notre arrivée, vers 9.30 a.m. une pangonia commence à tourner autour de nous. Elle commence par s'arrêter sur ma jambe et percer le pantalon, mais n'ayant probablement pas trouvé la chose à son goût, elle me quitte et se met sur la jambe d'un noir. Je dis à ce dernier de ne pas bouger, en lui promettant une bonne récompense. La mouche enfonce d'abord sa trompe sur la crête du tibia, mais elle en ressort immédiatement et choisit un autre endroit, sur le côté de la jambe, où elle enfonce de nouveau sa trombe, en s'appuyant d'abord sur ses pattes antérieures et ensuite sur ses pattes postérieures également. Un mouvement de mon chien effraye la mouche et elle retire vite sa trombe. On l'attrape. C'est une femelle. Dans son abdomen complètement vide et transparent on voit bouger un peu de sang liquide. A la place de la première piqûre (avortée) on voit perler une gouttelette de sang; de la deuxième piqûre il s'écoule plusieurs gouttes. La 'victime' me décrit ses sensations au moment de la piqûre: 'C'est comme si l'on enfonçait une aiguille,' en ajoutant que cette piqûre est beaucoup plus douloureuse que celle du tsé-tsé.

Nous restons encore pendant quelque temps sur place, mais sans aucune nouvelle aventure, et nous partons chercher fortune ailleurs. A la lisière même de la forêt, nous attendons et voyons voler autour de nous plusieurs pangonia, et nous nous arrêtons de nouveau. Bientôt une pangonia s'arrête sur mon soulier et tâche de le percer, mais n'y parvenant pas, elle le quitte, et se met sur mon chien qui fait immédiatement un écart très brusque. La mouche déménage alors sur le pied d'un noir et, tout en planant, elle commence à choisir un endroit convenable. Elle enfonce d'abord le bout de la trombe,



mais le retire immédiatement; enfonce sa trombe dans un autre endroit, la sort de nouveau et l'enfonce de suite dans un troisième endroit. Cette fois-ci définitivement, et s'appuyant sur ses pattes antérieures d'abord, et sur ses pattes postérieures ensuite. Elle enfonce environ la moitié de la trombe, c'est à dire en dépassant l'extrémité des stylets, et commence à sucer. Le noir, qui n'a pas bougé pendant tout ce temps, me dit que la sensation d'une aiguille enfoncée a justement cessée au moment du début de la succion. On voit peu à peu apparaître du sang liquide dans l'abdomen de la mouche. En suçante, cette dernière reste appuyée sur ses pattes. Subitement la mouche retire sa trombe et s'envole si brusquement que nous n'avons pas eu le temps de l'attraper. On reconnaît les deux endroits avortés par une gouttelette de sang; de l'endroit de la piqûre définitive il s'écoule plusieurs gouttes de sang, comme après la piqûre d'un doigt par une aiguille. J'ai examiné, dans l'après midi et le lendemain, les piqûres de ces deux hommes et je n'y ai constaté aucun signe d'inflammation. Il est vrai que la peau des noirs et surtout celle des pieds et des jambes n'est pas précisément bien délicate.

Deux autres hommes furent également piqués par les pangonia, dans l'après midi, et me donnèrent des preuves à l'appui : gouttelettes de sang aux jambes, et deux pangonia tachetées de sang; mais j'ajouterai que dans les deux cas, il s'agissait de piqûres provoquées pour ainsi dire : alléchés par le beau cadeau reçu par les deux blessés du matin, les deux autres ont imité leur exemple, en se tenant tranquilles, sans bouger, pour permettre aux pangonia de les piquer.

Différents auteurs considèrent la longueur excessive de la trombe des pangonia comme un obstacle à la piqûre. Mais cet obstacle n'est qu'apparent, d'après ce que j'ai vu dans les deux cas cités. C'est que la pangonia ne pique pas là où se trouve sa tête, mais à l'endroit où se trouve le bout de sa trombe. Aussi, dans un des cas décrits, la mouche s'étant posée sur le cou du pied, elle a enfoncé sa trombe, en ligne droite, dans le bas de la jambe, en laissant sous sa trombe un espace vide. Dans l'autre cas cité, s'étant posée sur la jambe même, la mouche a enfoncé sa trombe, *en la courbant un peu*, beaucoup plus haute et s'attirant légèrement ensuite. Comme dit, une partie de la trombe—environ la moitié—reste en dehors pendant

la succion. Toutefois, la longueur de la trombe au-delà des organes perforateurs, doit rendre la piquûre plutôt laborieuse et lente, et la moindre secousse doit plutôt déranger la mouche.

Que les pangonia piquent au vol, sans s'appuyer sur les pattes, cela est possible, d'autant plus qu'elles ont l'habitude de planer, mais dans les deux cas cités, les mouches s'appuyaient sur leurs pattes déjà au commencement de la piquûre, c'est à dire avant le commencement de la succion.

Quoiqu'il en soit, les pangonia, du moins la *P. zonata* et la *P. sp.* ? non seulement *peuvent* piquer, mais le font parfois; quoique d'autre part, elles semblent être peu avides de sang, autant que je puisse me permettre de le conclure de mes quelques trop rares observations. Et quand, parmi les supplices de l'enfer, Dante cite également celui des piquûres par des taons avec de longs dards, ce n'est pas seulement une figure poétique, mais une réalité.

Quant à la relation intime qui existerait, d'après les indigènes et d'après l'époque de l'année, entre les pangonia et certaines plantes,\* et notamment la Boraginée (sp. '*Nafimbia*'), je ne saurais pas me prononcer pour le moment d'une manière catégorique. J'espère que j'aurai prochainement l'occasion d'élucider cette question.

*Avril 1918.*

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\* Other plants submitted by Dr. Schwetz for determination were forwarded to The Director of the Royal Botanical Gardens, Kew, Sir David Prain, C.M.G., who very kindly gave the following names:—

1. *Acanthus montanus*, J. ANDS.
2. *Blepharis* sp.
3. *Wibisfeldia subviridis*, C. B. Cl.
4. *Mellera lobulata*, S. MOORE. [ED.]

# NEW WEST AFRICAN CERATOPOGONINAE

BY

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*(Received for publication 20 November, 1918)*

## PLATE VIII

The small or minute Chironomid flies forming the sub-family Ceratopogoninae are of considerable economic interest, as a number of species are known to suck blood. They are found in almost all parts of the world, and in some localities, which are by no means limited to tropical or sub-tropical regions, they are most troublesome and persistent in their attacks on man. Comparatively little is yet known of the Ethiopian fauna, few species have been described, and, so far as I am aware, no information regarding the early stages of any species from this region has hitherto been published. Particular interest, therefore, attaches to the species of *Forcipomyia* described below, the larvae of which were found and reared at Accra by Dr. Ingram, W.A.M.S., who also made careful observations on the early stages of this midge.\* The information he supplied is given on page 297. The interest in the species is enhanced by the fact that, given favourable opportunities for attack, its larvae prey upon the larvae of mosquitoes breeding in rot-holes in trees. In West Africa the larvae of several species of *Stegomyia*, including those of the carrier of yellow fever (*S. fasciata*, Fabr.), commonly occur in such situations. The main food of these midge larvae is the organic débris floating on the surface or stranded at the sides of the rot-hole, and in all likelihood

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\* A short account of the early stages by Dr. Ingram has just appeared in the Medical and Sanitary Report of the Gold Coast for the year 1917. The insect is referred to as a species of *Ceratopogon*, sens. str.

includes also dead insects and larval and pupal exuviae.\* It is most improbable that the *Forcipomyia* larvae could destroy active mosquito larvae, even although, as Dr. Ingram states, they swim freely. They rapidly destroy stranded larvae, however, and in nature, it is probable that they devour not only moribund larvae and pupae, but healthy pupae prior to eclosion and emerging adults. The food of the adult was not definitely ascertained, but is probably similar to that of the larva. Records of *Ceratopogoninae* attacking other insects are accumulating, and some members of the genus *Culicoides* are known to suck the juices of living mosquitoes. It is possible, therefore, that the imagines also may attack the mosquito fauna of the rot-holes, and that to some extent *Forcipomyia ingrami*, sp. n., in both its larval and adult stages, may act as one of the natural controls of these mosquitoes.

I desire to extend my sincere thanks to Dr. Ingram for giving me the opportunity of examining and describing this interesting little insect and for allowing me to make use of his notes. I also wish to thank Dr. G. A. K. Marshall, Director of the Imperial Bureau of Entomology, for his kindness in sending me examples of *F. castanea*, Walk., for comparative purposes.

The types and co-types of the two species herein described have been placed in the collection of the Liverpool School of Tropical Medicine.

#### Genus FORCIPOMYIA, Meig.

##### *Forcipomyia ingrami*, sp. n.

(Plate VIII, figs. 1-10)

A minute dark brown fly with yellowish scutellum, unicolorous wings and pale yellowish-brown legs.

LENGTH (two ♂s, two ♀s) ♂ 1.8 mm., ♀ 1.4 mm., length of wing, ♂ 1.2 mm., ♀ 1.1 mm.; length of antennae, ♂ 0.8 mm., ♀ 0.5 mm.

FEMALE: *Head* dark brown, the occipital region sparsely clothed with ochraceous hairs; clypeus prominent, bearing moderately long yellowish-brown hairs; eyes large, reniform, contiguous in the middle dorsal line. Proboscis about as long as the head, its component

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\* Pratt records the larvae of *Ceratopogon* (= *Culicoides*) *guttipennis*, Coq. feeding on dead mosquito and other insect larvae and upon cast larval and pupal skins.

organs, other than the labium, strongly chitinised and adapted for piercing; labium somewhat fleshy, pale brown in colour with sparsely arranged ochraceous hairs. Palpi (Plate VIII, fig. 10) yellowish-brown with pale hairs; each composed of five segments, the third segment elongate—more than twice the length of any other two segments taken together—and swollen on the inner lateral basal third; sensory organ in the swollen portion of the third segment communicating with the exterior by a relatively wide, deep circular pit containing numerous minute hairs. Antennae (Plate VIII, fig. 7) each composed of fifteen segments (including the reduced segment preceding the torus), testaceous, basal segments dark brown; segments three to ten spherical or oval, spherical at the base of the flagellum and gradually lengthening towards the tenth segment; eleventh to fourteenth segments cylindrical, each from two to three times as long as the greatest breadth; terminal segment larger and broader produced at the apex into a minute nipple-like process. Antennal hairs dark brown, arranged in whorls of ten on all but the last segment; segments eleven to fifteen with short pale hairs scattered over the surface. Delicate slightly curved spines occur on certain of the flagellum segments; they are present on at least all the segments up to and including the eighth\* (= tenth antennal segment), and are arranged in two admedian pairs (one dorsal, one ventral) on the anterior third of the segments. *Thorax* dark brown, broad in front gradually narrowing towards the scutellum; clothed with golden-brown hairs, which are longer and more numerous posteriorly, and with scattered dark bristles on the margins. Scutellum paler in colour with numerous long golden-brown bristles. Pleurae rather paler than the disc. Post-scutellum dark chestnut-brown, nude. *Wings* (fig. 1) unicolorous, densely clothed with brown decumbent hairs which are darker and more numerous anteriorly. Costa, first and third longitudinal veins and basal portion of the fourth longitudinal vein thicker, darker and bearing longer hairs than the remaining veins. The two small cells or interspaces situated near the middle of the upper margin of the wing,

\* Since writing the above further material has been received from Dr. Ingram. Spines occur on *all* the flagellum segments, but those on the last four segments are much smaller and more numerous than those on the basal segments and are scattered over the surface of each.

formed by fusion in the central region of the first and third longitudinal veins, are unequal in size and ill-defined; the proximal

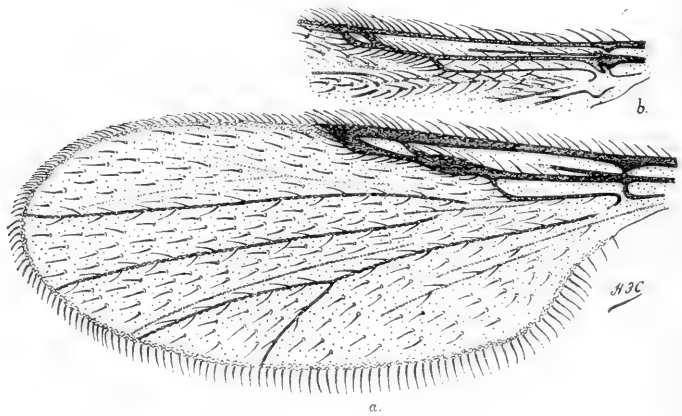


FIG. 1. *Forcipomyia ingrami*, sp. n.

a. Wing of female ( $\times 75$  circa); b. Upper basal portion of wing of male ( $\times 65$  circa). The hairs on the anterior portion of the wing, so far as the apical third, are much more numerous than is shown.

interspace is most minute, and is exceedingly difficult to distinguish. Rami of the fourth longitudinal vein very long, the base of the fork and the petiole obsolete. Halteres cream-coloured. Legs (fig. 2)

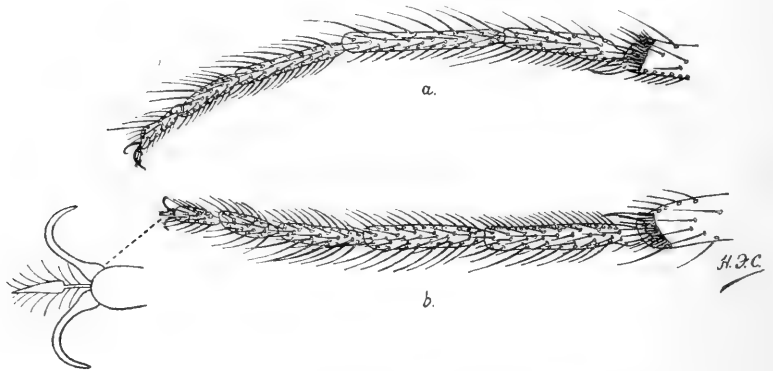


FIG. 2. *Forcipomyia ingrami*, sp. n.

a. Hind tarsus of male; b. Hind tarsus of female ( $\times 110$  circa).

yellowish-brown, somewhat thickly clothed with relatively long ochraceous hairs. Femora unarmed. Fore tibiae with apical ventral spurs; hind tibiae each with an apical spur and two obliquely trans-

verse rows of bristles—the anterior row composed of seven rather coarse bristles, the posterior row of fourteen or fifteen shorter, finer ones. First tarsal segments of all legs approximately  $1\frac{1}{3}$  times the length of the second segments. Claws well developed, simple. Empodium hairy, nearly as long as the claws. *Abdomen*: dorsum slightly darker than the thorax clothed with yellowish hairs which are longer at the sides and apex; cerci hairy and about half as long as the terminal segment. Venter yellowish-grey. Spermathecae two, strongly chitinised, spherical.

MALE: Less robust in build than the female and differing as follows:—*Head*: third segment of palpus (Plate VIII, fig. 9) less swollen basally, the sensory cup containing but few (apparently three or four) relatively short stout hairs which are dilated at their apices. Antennae (Plate VIII, fig. 8) longer, plumose; tori very large sub-spherical; basal portion of third segment (i.e. first flagellum segment) elongate, cylindrical, apical portion dilated bearing a whorl of ten relatively short hairs; segments four to eleven inclusive spherical or sub-spherical, each with hairs (thirty to forty in number) arranged in a median transverse whorl; twelfth segment greatly elongated, the basal portion smaller but resembling that of the preceding segments in form, the apical portion very long and narrow, cylindrical; thirteenth and fourteenth segments somewhat similar in shape to the twelfth segment, but only about half as long; terminal segment broad and flattened without a distinct whorl of hairs; last four segments, taken together, almost equal to the combined lengths of the first nine flagella segments. *Wings* (fig. 1) longer, narrower and less densely clothed with hairs than in ♀; first and third longitudinal veins separating immediately before the costa and forming with that vein a single small cell. *Legs* (fig. 2) rather paler than in ♀; first tarsal segments of the fore and middle legs slightly longer than the second segments; hind metatarsi each approximately three-quarters the length of the following tarsal segment. *Abdomen* more slender than that of the ♀, and more densely clothed (particularly on the apical segments) with longer hairs.

MALE HYPOPYGIUM (fig. 3). Side pieces short bearing numerous very long coarse hairs on both dorsal and ventral surfaces; inner margin convex with a somewhat prominent hair or bristle

arising near the middle. Basal lobes of side pieces well developed, each with four or five short strong hairs arising from the apical margin and a shorter spine-like hair near the middle of the inner margin. Terminal clasp segment stout, rather more than two-thirds the length of the side piece; dorsal surface depressed at the apex which is shallow and spoon-like. Penis sheath broad at the base, narrowing to a bluntly rounded apex but slightly constricted just before the distal extremity.

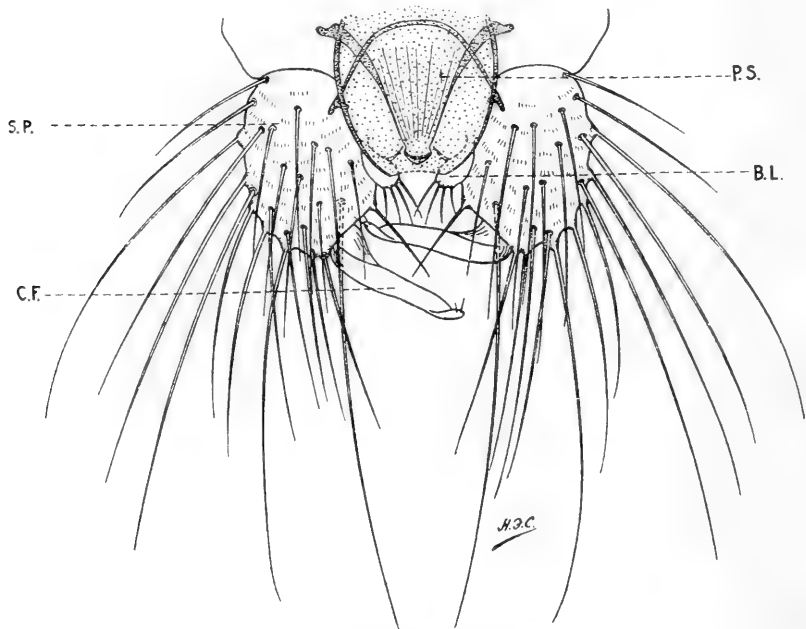


FIG. 3. *Forcipomyia ingrani*, sp. n.

Male hypopygium, ventral view ( $\times 240$  circa). S.P., side piece; C.F., clasp filament; B.L., basal lobe of side piece; P.S., penis sheath.

LARVA (Plate VIII, figs. 1-4). *Length* 2.5 mm. to 3.0 mm. A creamy white, eucephalus, fleshy-bodied, bristly creature, with pseudopods on the first and last segments. *Head* strongly chitinised, more or less conical in form, without distinct eye spots and bearing a number of hairs and spines as shown in the figure. Antennae in the form of simple uni-segmented curved pointed processes arising from narrowly separated tubercles situated on the vertex. Mandibles powerful, each armed with a number (apparently



fourteen) of strong chitinous teeth and a few relatively long basal spinous processes. *Body* composed of twelve visible segments, each with an armature of bristles or spines, as follows:—A pair of tuberculate, spear-shaped, admedian dorsal spines, a pair of small, curved, tuberculate, hairy dorso-lateral spines, four relatively stout bristles on each side and a pair of minute bifurcate or trifurcate sub-ventral hairs. The dorsal spear-like spines are most conspicuous, and are possibly characteristic; excluding the tubercular base, each consists of a narrow proximal portion and a broad blade-like distal portion, the two portions being more or less equal in length, except in the anal pair, which are very long owing to great extension of pedicle. The pair of spines on the first segment are somewhat rudimentary, and are very similar in size and shape to the cephalic pair which are situated a short distance behind the antennae. The posterior extremity of the twelfth segment is produced sub-dorsally into a relatively large papilla, which bears a pair of small branched hairs and a pair of simple hairs—the latter arising from cylindrical tubercles; medially this portion of the segment is extended into a large semi-membranous triangular process, the sides of which are fringed with short hairs; immediately below this process are two pairs of small gills. Each pair of pseudopods is fused into a single organ, but coalition of the anal pair would seem to be less complete than that of the pro-thoracic pair, as the armature of hooks is interrupted in the middle line. The anal pseudopod occupies the whole of the ventral extremity of the twelfth segment, which is evidently capable of invagination to a considerable extent (c.f. Plate VIII, figs. 2 and 3). When extended the apical ventral margin of this segment is seen to be covered with numerous minute teeth or spines surmounted by two more or less distinct groups of strong chitinous hooks. The latter are arranged in a double row, those forming the more ventral series being smaller and numbering five in each group, while the upper row consists of considerably larger hooks arranged in two sets of four hooks each.

**PUPA** (Plate VIII, fig. 5). *Length* 3·0 mm. This stage of the insect is slightly darker in colour than the larva (judging by the preserved specimens), and possesses a distinctly granular integument. Its armature of spines and bristles is very weak, and it is apparently entirely free of the larval skin since no trace of exuviae

can be detected on the distal segments of the specimens available. The respiratory trumpets (Plate VIII, fig. 6) are beautiful though complex structures, and their form and external morphology may best be appreciated by examining the figure. The *thorax* bears a number of tubercles (particularly on the dorsal surface) and is extended posteriorly over the middle of the first abdominal segment in the form of a relatively large, conical papilla. The thoracic tubercles are arranged as follows:—Three small granular dorso-admedian tubercles and two larger smooth ventral ones on the anterior margin; three small antero-dorso-median tubercles arranged in the form of a backwardly-directed triangle; two large conical bristle-bearing tubercles posterior to the air-trumpets; a lateral pair situated slightly behind the last-named tubercles; a pair at the base and a very small pair near the middle of the papilla-like extension of the thorax. *Abdomen* broad at the base, gradually narrowing towards the apex, with minute tuberculate bristles at the sides and a pair of minute admedian hairs on each segment. The ninth segment is elongate, and is produced into two long, pointed, finger-like processes, each of which bears at its base a small dorsal rumule.

HABITAT: Accra, Gold Coast, 1918. Dr. A. Ingram.

This little midge, which I have much pleasure in associating with its discoverer, does not appear to be closely related to any members of the genus *Forcipomyia* yet described from the Ethiopian region. Four species\* of *Forcipomyia*, known from females only, occur in West Africa, and in this sex it may readily be distinguished from all of these—except *F. lefanui*, Carter—by the metatarsi of the hind legs being longer than the second tarsal segments. *F. lefanui* is a smaller and darker insect, and the hind metatarsi are relatively much longer than in *F. ingrami*; but the most obvious differential characters perhaps are those supplied by the neuration of the wings. In *F. lefanui* the distal extremity of the third longitudinal vein is narrowly separated from, and extends for some distance more or less parallel to, the costa and joins the anterior margin of the wing near the apical third, whereas in *F. ingrami* the distal portion of the third vein is short and joins the anterior margin near the middle. Two species—*F. tavetae* and

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\* *F. castanea*, Walk., *F. incomptifeminitus*, Aust., *F. inornatipennis*, Aust., and *F. lefanui*, Carter.

*F. tangae*—described by Kieffer from East Africa, also have the hind metatarsi longer than the second tarsal segments, but from these *F. ingrami* apparently differs considerably in its general facies and wing venation.

Dr. Ingram's observations on the early stages of this insect are of considerable value and interest, as will be gathered from the following information which he has supplied.

The *Forcipomyia* larvae were first noticed by Dr. Ingram while carrying out experiments with the larvae of *Stegomyia fasciata*, Fabr. The conditions under which the experiments were conducted were such that it was necessary to protect the larvae against the ravages of ants, spiders, etc., but in spite of various precautions being taken, the mosquito larvae disappeared. Ultimately Dr. Ingram found that they were 'being eaten by some small and active larvae with black heads. Five or six of these larvae quickly pulled a stranded *S. fasciata* larva to pieces—they appeared to feed upon any organic material they came across and paid special attention to the *S. fasciata* larvae when they were motionless . . . ' The *Forcipomyia* larvae are not strictly aquatic, for although they swim admirably they do not seem to like water and prefer wandering about just above the water-line. 'Upon flooding the surface . . . with water to the depth of half an inch they immediately made for the sides of the receptacle and crawled above the water-line, remaining there till all the water had drained away. Apparently their usual breeding places are rot-holes in trees, as I have found them immediately after moistening the débris scraped out of rot-holes in Flamboyant trees.' In the laboratory, however, Dr. Ingram never observed them until his experiments had continued for two or three weeks—that is until a considerable amount of organic material had accumulated from the occasional emptying of jars containing *S. fasciata* larvae. 'The pupae are very inert, and were usually adherent to the sides of the receptacle above the water-line; when the depth of the water was increased so as to submerge them they became detached and showed feeble movements in the water. The larval stage seems to vary in duration with the amount of food supply; the pupal stage lasts about thirty-six hours.' Dr. Ingram states that up to the present he has been unable to discover the eggs of this little fly.

## Genus CULICOIDES, Latr.

*Culicoides ochrothorax*, sp. n.

A small dark brownish-grey midge with bright ochraceous mesonotum and spotted wings; fore and middle legs with a conspicuous broad pale band enveloping the femoro-tibial joint, hind tibiae entirely ochraceous, fore tarsi brownish, middle and hind tarsi ochraceous.

LENGTH (one specimen) 1.4 mm.; length of wing 1.1 mm.; length of antennae 0.7 mm.

FEMALE. *Head* dark brown or brownish-grey with dark hairs; clypeus shining dark reddish-brown, hairy; eyes black, narrowly separated dorsally. Proboscis about as long as the head, the labium pale with yellowish hairs. Palpi pale brown, densely clothed with brownish hairs; last two segments somewhat geniculate, third segment relatively broad and apparently of peculiar structure. This segment seems to be partially divided—from the apex almost to the base—and bears apically and laterally a number of minute modified hairs, each of which resembles a soup-ladle in miniature. Second segment long and narrow, rather longer than the third; fourth and fifth segments short, their combined lengths almost equal to that of the second. *Antennae*: Torus dark brown with a few short hairs; flagellum, except the last two or three segments which are somewhat testaceous, paler brown with whorls of yellowish-brown hairs. Flagellum segments elongate-ovoid about two and a half times as long as the greatest width, gradually becoming narrower, longer and more cylindrical towards the apex of the antenna; last segment broader than the preceding segment, somewhat flattened and terminating in a small, hairy styliiform process. The antennae are provided with short straight spines—difficult to see—which can only be detected with certainty, in the limited material available, on the seventh segment. *Thorax*: Dorsal surface bright ochraceous with two small grey shoulder spots, a greyish-ochraceous median line extending from the anterior margin to the middle of the scutum and a relatively broad greyish-ochraceous median stripe extending from the posterior extremity of the median line to the scutellum. Dorsum sparsely clothed with brown and yellowish-brown hairs. Scutellum brownish-grey, becoming somewhat ochraceous near the centre of the

posterior margin, bearing three long yellowish-brown border bristles. Post-scutellum dark brown, nude. Pleurae ochraceous above, dark brown below, the two colours sharply separated along the middle line. *Wings* (fig. 4) brownish-grey, darker along the anterior border, with two relatively large white spots anteriorly—one covering the apex of the third longitudinal vein, the other covering the junction of the third and first longitudinal veins and the radio-medial cross vein. The apex of the wing is narrowly pale. Three other pale spots are present, but are smaller and much less conspicuous than the two costal spots mentioned above. Two of these are situated on the posterior border of the wing, one between the branches on the fifth longitudinal vein, the other immediately

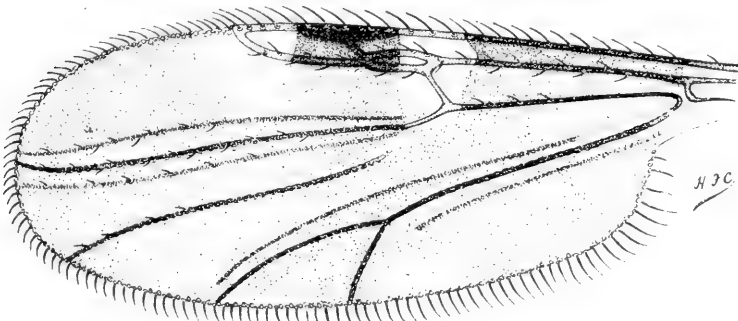


FIG. 4. *Culicoides ochrothorax*, sp. n.  
Wing of female ( $\times 75$  circa).

behind the lower branch; they are ill-defined and can scarcely be distinguished when held at certain angles. The remaining pale area embraces the extreme base of the wing. Venation as shown in the figure, the small cells formed by the first and third veins distinct, the distal cell large and widely open. Extreme base of lower branch of fourth vein obsolete. Wings completely covered with minute upright setae; longer hairs only present on the thicker veins situated near the anterior margin, and on some of the veins and folds near the apex. Halteres cream coloured. *Legs*: Fore and middle femora dark brown basally, ochraceous apically, the latter colour occupying one-third and one-half the length of the respective limbs; hind femora dark brown. Fore and middle tibiae

ochraceous basally, dark brown apically, the former colour occupying one-third and one-half the length of the respective limbs; hind tibiae ochraceous. Fore tibiae each armed with a short stout ventral spine at the distal extremity; middle tibiae unarmed; hind tibiae each with a short blunt spur and two transverse rows of bristles apically—the distal row composed of four relatively long stout bristles, the inner or proximal row of about twenty much shorter, finer bristles. Fore tarsi pale brown, middle and hind tarsi ochraceous, metatarsi of the fore and middle legs each three to four times the length of the following segment, hind metatarsi each about twice the length of the second tarsal segment. Claws simple and equal. Empodium minute, less than half the length of the claws. *Abdomen* dark brown, the basal segments with narrowly pale hind margins, clothed with short dark hairs. Ventral surface slightly paler than the dorsum. Cerci yellowish.

HABITAT: Ashanti, Gold Coast, 1913, Dr. H. F. Hamilton.

*C. ochrothorax* is a well-marked species, and may be readily distinguished from its known African congeners, if not from all other known members of the genus, by the coloration of the mesonotum. The type and sole example was included in a small collection of *C. grahamii*, Aust., forwarded by Dr. Hamilton; all specimens bore the same data.

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## EXPLANATION OF PLATE

*Forcipomyia ingrami*, sp. n.

- Fig. 1. Head and first thoracic segment of larva ( $\times 120$  circa).
- Fig. 2. Anal extremity of larva with posterior pseudopod retracted ( $\times 120$  circa).
- Fig. 3. Anal extremity of larva, ventral view, showing pseudopod exerted ( $\times 120$  circa).
- Fig. 4. Mandible of larva ( $\times 370$  circa).
- Fig. 5. Pupa, dorsal view ( $\times 25$  circa).
- Fig. 6. Respiratory trumpet of pupa ( $\times 185$  circa).
- Fig. 7. Antenna of female (small basal segment not shown) ( $\times 120$  circa).
- Fig. 8. Antenna of male (small basal segment not shown). ( $\times 120$  circa).
- Fig. 9. Male palpus ( $\times 185$  circa).
- Fig. 10. Female palpus ( $\times 185$  circa).







# STUDIES IN THE TREATMENT OF MALARIA

## XVIII. A COMPARISON OF THE VALUE OF *CONTINUOUS* AND *INTERRUPTED* QUININE ADMINISTRATION IN SIMPLE TERTIAN MALARIA

### (SECOND COMMUNICATION)

BY

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AND

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*Undertaken at the request of the War Office*

*(Received for publication 11 November, 1918)*

In a previous study (1918) we have shown to what extent relapses can be prevented during the course of the treatment by *interrupted* administration of quinine, i.e. administration on each of two consecutive days weekly. The present series of observations were conducted in order to ascertain whether a certain amount of quinine weekly is better given in small doses divided over six or seven days each week (*continuous* treatment) or in larger doses given on two consecutive days only each week (*interrupted* treatment). For example, assuming the total amount of quinine to be given each week be grains 30, is it better to administer grains 5 on each of six consecutive days, or grains 15 on each of two consecutive days, weekly?

To determine this question two series of observations were conducted:—

1. Total weekly dose of quinine sulphate, grains 30.
  - A. Quinine sulphate grains 5 on each of six consecutive days weekly, for eight weeks.
  - B. Quinine sulphate grains 15 on each of two consecutive days weekly, for eight weeks.
2. Total weekly dose of quinine sulphate, grains 90.
  - C. Quinine sulphate grains 15 on each of six consecutive days weekly, for eight weeks.
  - D. Quinine sulphate grains 45 on each of two consecutive days weekly, for eight weeks.

All the cases were adult males infected for the most part either in Macedonia or in East Africa. In every instance a diagnosis of simple tertian malaria was made microscopically, and in all cases parasites were present in the blood on the day treatment was commenced. Blood examinations in the majority of cases were made daily until parasites disappeared from the blood, and subsequently once weekly and also whenever the temperature reached 100° F. or over, which in this, as in previous papers, is regarded as a febrile paroxysm—slight elevations of temperature not reaching 100° F. being ignored.

The records of the observations are given in the tables at the end of the paper. In these tables and in the charts:

o	= absence of fever and parasites.
1, 2, etc.	= number of parasitic febrile relapses weekly.
1*, 2*, etc.	= number of non-parasitic febrile attacks weekly.
P.	= non-febrile parasitic relapse.
Q.O.	= quinine sulphate orally.
T.	= simple tertian trophozoites or schizonts.
G.	= simple tertian gametes.
cr.	= malignant tertian gametes.
Neg.	= no parasites found.

NOTE.—A rise of temperature above 100° F., of which the nature is unknown, is termed a *febrile attack*. A similar rise of temperature accompanied by parasites in the blood at the time, or within three days, is termed a *parasitic febrile relapse* or *true relapse*. The term *paroxysm* is used indifferently to denote any febrile disturbance of 100° F. or more.

As we have pointed out elsewhere, the effect of any treatment may be considered from two points of view: (1) the *palliative* action, i.e. the degree to which symptoms are controlled, and the blood kept free from parasites during the treatment; and (2) the *curative* action, i.e. whether or no relapses occur during the observation period\* after cessation of treatment. In order that the palliative results obtained in the various series of observations may have a comparative value, it is necessary to express the number of cases having true relapses and of those having febrile attacks, as percentages of the total cases undergoing treatment in any particular week. In Tables I-VIII the following sets of figures, each having a comparative value, are given:—

1. The number of cases which had each week, over a period of eight weeks, parasitic febrile relapses, expressed as percentages of all cases treated.
2. The number of parasitic febrile relapses experienced each week, over a period of eight weeks, by each parasitic febrile relapse case.
3. The number of cases which had each week, over a period of eight weeks, febrile paroxysms (parasitic and non-parasitic), expressed as percentages of all cases treated.
4. The number of febrile paroxysms (parasitic and non-parasitic) experienced each week, over a period of eight weeks, by each febrile (parasitic and non-parasitic) case.

### GRAINS 30 SERIES

#### A. Grains 5 on each of six consecutive days weekly (Cases 923-969)

In four of the forty-seven cases treatment was commenced during an apyrexial period. In forty of the remaining forty-three the temperature fell to normal in one to five days, whilst in three cases (Nos. 925, 967 and 969) the temperature was uncontrolled.

In thirty-four cases parasites disappeared from the cutaneous blood in one to five days, whilst in the remaining thirteen cases parasites persisted practically throughout treatment (*vide* Chart 946 and Table XI).

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\* This, as in all our previous papers, is 60 days—an entirely arbitrary period.

*Relapses.*

*During treatment.* In eight of the forty-seven cases, owing to the severity of the relapses and the grave clinical condition of the patients, it was found impossible to continue the treatment for the full period of eight weeks, e.g. in Case 962 treatment had to be changed in the seventh week, in Cases 963 (*vide* Chart) and 964 in the fifth week, in Cases 965 (*vide* Chart) and 966 in the third week, and in Cases 967 to 969 in the second week. Consequently the number of cases under treatment was in the first week 47, and in the eighth week 39 (Table XI). The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 15·1 per cent. of cases treated, (2) non-parasitic febrile attacks 10·9 per cent., and (3) febrile paroxysms (both parasitic and non-parasitic) 26·0 per cent. (Tables I and II).

TABLE I.

Summary of results of oral administration of quinine sulphate in solution, grains 5, on each of six consecutive days weekly for 8 weeks.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>47</b>	<b>47</b>	<b>44</b>	<b>42</b>	<b>42</b>	<b>40</b>	<b>40</b>	<b>39</b>
Number of cases having parasitic febrile relapses ...	5	13	15	6	5	6	3	0
Number of cases having non-parasitic febrile attacks ...	1	4	3	2	4	9	8	5
<b>Grand total of all febrile cases ...</b>	<b>6</b>	<b>17</b>	<b>18</b>	<b>8</b>	<b>9</b>	<b>15</b>	<b>11</b>	<b>5</b>
Total number of parasitic febrile relapses	12	32	24	11	13	14	7	0
Total number of non-parasitic febrile attacks	1	6	7	3	7	13	11	10
<b>Grand total of all febrile paroxysms ...</b>	<b>13</b>	<b>38</b>	<b>31</b>	<b>14</b>	<b>20</b>	<b>27</b>	<b>18</b>	<b>10</b>

TABLE II.  
Analysis of TABLE I.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ... ..	10.6	27.7	34.1	14.3	11.9	15.0	7.5	0	15.1
Number of parasitic febrile relapses per parasitic febrile relapse case ... ..	2.4	2.5	1.6	1.8	2.6	2.3	2.3	0	1.9
Percentage of all febrile (parasitic and non- parasitic) cases per cases treated ...	12.8	36.2	40.9	19.0	21.4	37.5	27.5	12.8	26.0
Number of all febrile (parasitic and non- parasitic) paroxysms per febrile case ...	2.2	2.2	1.7	1.7	2.2	1.8	1.6	2.0	1.9

*After treatment.* Thirty of the thirty-nine cases observed after cessation of treatment relapsed within the sixty-day observation period. Parasites reappeared in one to fifty-eight days, and febrile relapses occurred in one to twenty-six days, after cessation of treatment. In eight of the cases (Nos. 962-969) the full course of treatment was not completed, as owing to relapses it was found necessary to alter the treatment. These cases therefore should be added to the cases that relapsed, making the total number of failures thirty-eight (81 per cent.). In one of the nine cases which did not relapse the observation period after treatment was less than sixty days, viz., in Case 932, twenty-one days (Table XI). Consequently the minimum number of relapses is 81 per cent. and the possible maximum 83 per cent.

#### B. Grains 15 on each of two consecutive days weekly (Cases 970-1034)

In nine of the sixty-five cases treatment was commenced during an apyrexial period; in the remaining fifty-six cases the temperature fell to normal in one to five days. In forty cases parasites disappeared from the cutaneous blood in one to four days; in the remaining twenty-five cases the examinations were too infrequent to give an exact figure (Table XII).

#### *Relapses.*

*During treatment.* In all the sixty-five cases treatment was continued during the full period of eight weeks, although several of

the cases had many parasitic rigors during treatment (*vide* Chart 980). The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 7.5 per cent. of cases treated, (2) non-parasitic febrile attacks 9.4 per cent., and (3) febrile paroxysms (both parasitic and non-parasitic) 16.9 per cent. (Tables III and IV).

TABLE III.

Summary of results of oral administration of quinine sulphate in solution, grains 15, on each of two consecutive days weekly, for 8 weeks.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>65</b>	<b>65</b>	<b>65</b>	<b>65</b>	<b>65</b>	<b>65</b>	<b>65</b>	<b>65</b>
Number of cases having parasitic febrile relapses ...	0	2	11	3	5	6	6	6
Number of cases having non-parasitic febrile attacks ...	6	8	5	6	5	2	9	7
<b>Grand total of all febrile cases ...</b>	<b>6</b>	<b>10</b>	<b>16</b>	<b>9</b>	<b>10</b>	<b>8</b>	<b>15</b>	<b>13</b>
Total number of parasitic febrile relapses	0	5	26	5	6	6	9	14
Total number of non-parasitic febrile attacks	10	10	8	9	6	3	10	9
<b>Grand total of all febrile paroxysms ...</b>	<b>10</b>	<b>15</b>	<b>34</b>	<b>14</b>	<b>12</b>	<b>9</b>	<b>19</b>	<b>23</b>

TABLE IV.

Analysis of TABLE III.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ...	0	3.1	17.0	4.6	7.7	9.2	9.2	9.2	<b>7.5</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ...	0	2.5	2.4	1.7	1.2	1.0	1.5	2.3	<b>1.6</b>
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated ...	9.2	15.4	24.6	13.9	15.4	12.3	23.1	20.0	<b>16.9</b>
Number of all febrile (parasitic and non-parasitic) paroxysms per febrile case ...	1.7	1.5	2.1	1.6	1.2	1.1	1.3	1.8	<b>1.5</b>



*After treatment.* Forty-nine of the sixty-two\* cases observed after cessation of treatment relapsed within the sixty-day observation period. Parasites reappeared in one to fifty-six days and febrile relapses occurred in one to fifty-six days. In three of the thirteen cases which did not relapse the observation period after treatment was less than sixty days, viz., in Case 1002, forty-two days; in Case 1027, fifty days; and in Case 1033, fifty-four days (Table XII). Consequently the minimum number of relapses is 79 per cent., and the possible maximum 84 per cent.

### GRAINS 90 SERIES

#### C. Grains 15 on each of six consecutive days weekly (Cases 1035-1083)

In five of the forty-nine cases treatment was commenced during an apyrexial period; in the remaining forty-four cases the temperature fell to normal within four days. In twenty-six cases parasites disappeared from the cutaneous blood in one to three days; in the remaining cases the examinations were too infrequent to give an exact figure (Table XIII).

#### *Relapses.*

*During treatment.* In one case (No. 1083), owing to the severity of the relapses, it was found necessary to alter the treatment at the end of the seventh week; in all others the treatment was continued for the full period of eight weeks. Consequently the number of cases under treatment was in the first week forty-nine, and in the eighth week forty-eight (Table XIII). The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 4.1 per cent. of cases treated, (2) non-parasitic febrile attacks 9.7 per cent., and (3) febrile paroxysms (both parasitic and non-parasitic) 13.8 per cent. (Tables V and VI).

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\* Three cases (Nos. 973, 1011 and 1029) were not observed after cessation of treatment.

TABLE V.

Summary of results of oral administration of quinine sulphate in solution, grains 15, on each of six consecutive days weekly for 8 weeks.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>49</b>	<b>49</b>	<b>49</b>	<b>49</b>	<b>49</b>	<b>49</b>	<b>49</b>	<b>48</b>
Number of cases having parasitic febrile relapses ...	1	1	3	2	2	2	3	2
Number of cases having non-parasitic febrile attacks ...	2	5	3	5	3	10	8	2
<b>Grand total of all febrile cases ...</b>	<b>3</b>	<b>6</b>	<b>6</b>	<b>7</b>	<b>5</b>	<b>12</b>	<b>11</b>	<b>4</b>
Total number of parasitic febrile relapses	1	3	8	3	2	4	7	3
Total number of non-parasitic febrile attacks ...	3	5	4	5	3	13	8	2
<b>Grand total of all febrile paroxysms ...</b>	<b>4</b>	<b>8</b>	<b>12</b>	<b>8</b>	<b>5</b>	<b>17</b>	<b>15</b>	<b>5</b>

TABLE VI.

Analysis of TABLE V.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated *	2.0	2.0	6.1	4.1	4.1	4.1	6.1	4.2	<b>4.1</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ...	1.0	3.0	2.7	1.5	1.0	2.0	2.3	1.5	<b>1.9</b>
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated ...	6.1	12.2	12.2	14.3	10.2	24.5	22.4	8.3	<b>13.8</b>
Number of all febrile (parasitic and non-parasitic) paroxysms per febrile case ...	1.3	1.3	2.0	1.1	1.0	1.4	1.4	1.2	<b>1.3</b>

*After treatment.* Twenty-nine of the forty-six\* cases observed after cessation of treatment relapsed within the sixty-day observation period. Parasites reappeared in one to fifty-six days and febrile relapses occurred in one to forty-five days after cessation of treatment. One case (No 1083) did not complete the full course of eight weeks' treatment as the condition was uncontrolled. This case, therefore, should be added to the cases that relapsed, making the total number of failures thirty (64 per cent.). In one of the seventeen cases which did not relapse the observation period after treatment was less than sixty days, viz., in Case 1078, fifty days (Table XIII). Consequently the minimum number of relapses is 64 per cent. and the possible maximum 66 per cent.

#### D. Grains 45 on each of two consecutive days weekly (Cases 1084-1157)

In thirteen of the seventy-four cases treatment was commenced during an apyrexial period; in the remaining sixty-one cases the temperature fell to normal within four days.

In fifty-eight cases parasites disappeared from the cutaneous blood in one to four days; in the remaining cases the examinations were too infrequent to give an exact figure (Table XIV).

#### *Relapses.*

*During treatment.* In all the seventy-four cases treatment was continued during the full period of eight weeks. The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 1·8 per cent. of cases treated, (2) non-parasitic febrile attacks 8·5 per cent., and (3) febrile paroxysms (both parasitic and non-parasitic) 10·3 per cent. (Tables VII and VIII).

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\* Two cases (Nos. 1040 and 1076) were not observed after treatment.

TABLE VII.

Summary of results of oral administration of quinine sulphate in solution, grains 45, on each of two consecutive days weekly for 8 weeks.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>74</b>	<b>74</b>	<b>74</b>	<b>74</b>	<b>74</b>	<b>74</b>	<b>74</b>	<b>74</b>
Number of cases having parasitic febrile relapses ...	0	0	4	1	2	1	2	1
Number of cases having non-parasitic febrile attacks ...	3	4	8	6	6	8	9	6
<b>Grand total of all febrile cases ...</b>	<b>3</b>	<b>4</b>	<b>12</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>11</b>	<b>7</b>
Total number of parasitic febrile relapses	0	0	7	2	4	1	3	1
Total number of non-parasitic febrile attacks ...	3	5	11	9	10	11	16	8
<b>Grand total of all febrile paroxysms ...</b>	<b>3</b>	<b>5</b>	<b>18</b>	<b>11</b>	<b>14</b>	<b>12</b>	<b>19</b>	<b>9</b>

TABLE VIII.

Analysis of TABLE VII.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ...	0	0	5.4	1.3	2.7	1.3	2.7	1.3	<b>1.8</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ...	0	0	1.7	2.0	2.0	1.0	1.5	1.0	<b>1.1</b>
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated ...	4.0	5.4	16.2	9.4	10.8	12.1	14.8	9.4	<b>10.3</b>
Number of all febrile (parasitic and non-parasitic) paroxysms per febrile case ...	1.0	1.2	1.5	1.6	1.7	1.3	1.7	1.3	<b>1.4</b>

*After treatment.* Fifty-seven of the seventy-one† cases observed after cessation of treatment relapsed within the sixty-day observation period. Parasites reappeared in one to forty-seven days, and febrile relapses occurred in three to forty-eight days after cessation of treatment. One case (No. 1091) relapsed after the expiration of the period, and is therefore not included among the relapses. In three of the fourteen cases which did not relapse the observation period was less than sixty days, viz., in Case 1115, thirty-one days; in Case 1141, forty days; and in Case 1144, fifty-four days (Table XIV). Consequently the minimum number of relapses is 80 per cent. and the possible maximum 85 per cent.

### COMPARISON OF RESULTS OBTAINED FROM THE VARIOUS TREATMENTS

#### A. Palliative

The primary object of these observations was, as we have already stated, to determine whether a certain total weekly amount of quinine is better given by the *continuous* or by the *interrupted* method; e.g. is a total weekly dose of grains 30 more efficacious when administered as grains 5 on each of six consecutive days weekly or as grains 15 on each of two consecutive days weekly? It will be seen from Table IX that when grains 30 were administered

TABLE IX.

Comparison of palliative results obtained from the different treatments.

	A	B	C	D
Weekly dose of quinine sulphate in grains	5 × 6	15 × 2	15 × 6	45 × 2
Percentage of parasitic febrile relapse cases per cases treated (average per week) ... ..	15.1*	7.5	4.1	1.8
Percentage of non-parasitic febrile relapse cases per cases treated (average per week) ... ..	10.9*	9.4	9.7	8.5
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated (average per week) ... ..	26.0*	16.9	13.8	10.3

\* As in 8 of the 47 cases in this series treatment had to be abandoned before completion of 8 weeks, this is only a minimum figure (*vide text*).

† Three cases (Nos. 1106, 1108 and 1109) were not observed after treatment.

as grains 5 on each of six days weekly, the average weekly number, over a period of eight weeks, of cases which had parasitic febrile relapses was 15·1 per cent. of cases treated, whereas when administered as grains 15 on each of two consecutive days weekly the percentage was only 7·5. Moreover, in eight of the forty-seven cases comprising the series in which the *continuous* treatment (i.e. grains 5 daily) was given, symptoms were not controlled and the method had to be abandoned; consequently 15·1 per cent. is only a minimum figure. In the grains 90 series the average weekly number, over a period of eight weeks, of cases which had parasitic febrile relapses was 4·1 per cent. when the *continuous* method was adopted and 1·8 per cent. with the *interrupted* method.

As we have previously pointed out, the efficacy of the various treatments regarded as palliatives must be judged from the percentage of cases having parasitic febrile relapses, as we know nothing of the real nature of the non-parasitic febrile attacks (*vide* Charts 949, 951, 1038 and 1087), which may or may not be malarial in nature. From this we conclude that, given a total weekly dose of quinine, it is better to divide it into two equal parts and administer one on each of two consecutive days weekly, than to divide it into six equal parts and administer one on each of six consecutive days.

If instead of parasitic febrile relapses we consider all febrile paroxysms (both parasitic and non-parasitic), we see that for the Grains 30 series the figure (26·0 per cent.) for the *continuous* method is higher than that (16·9 per cent.) for the *interrupted* method; for the Grains 90 series the figures are respectively 13·8 and 10·3 per cent. It is interesting to note in Table IX that the figure for the non-parasitic febrile attacks is practically constant for all four treatments, viz., about 10 per cent. If these non-parasitic febrile attacks were malarial, it might be expected that in the four treatments their relative frequency would be proportional to that of the parasitic febrile relapses; this, however, is not the case, e.g. the percentage of parasitic febrile relapses in Treatment A is eight times as great as in Treatment D, whereas that of the non-parasitic febrile attacks is only 1·3 times as great.

## B. Curative

In comparing the curative value of the various treatments we think it necessary, as considerable obscurity seems still to exist on the matter, to point out again that an observation period of definite duration after cessation of treatment is essential. In this, as in all our previous work, we have aimed at a post-treatment observation period of sixty days—a purely arbitrary limit—in those cases which did not relapse before the expiration of this period. In Series A, one case, which did not relapse, left hospital before the completion of the sixty days' observation period; in Series B, three cases; in Series C, one case; and in Series D, three cases. Consequently, in estimating the percentage of relapses which occurred within the sixty days' observation period two figures must be given: (1) the number of relapses actually observed: this represents the minimum number of relapses; (2) the number of relapses actually observed, plus the number of cases not relapsing but lost sight of before expiration of the sixty days' observation period: this represents the possible maximum number of relapses.

The curative results of the four treatments are given in Table X.

TABLE X.

Comparison of curative results obtained from the different treatments.

Series	Dose in grains	Duration of treatment	Number of cases observed after treatment*	Number of cases which relapsed within 60 days*	Number of cases not relapsing but observed for less than 60 days	Percentages of cases which relapsed	
						minimum	maximum
A	5 × 6	2 months	47	38	1	81	83
B	15 × 2	"	62	49	3	79	84
C	15 × 6	"	47	30	1	64	66
D	45 × 2	"	71	57	3	80	85

\* Including those cases in which treatment was abandoned as the condition was uncontrolled.

It will be seen that from this point of view there is little to choose between the various treatments, as in all four series the majority of the cases relapsed within sixty days of cessation of treatment.

### CONCLUSION

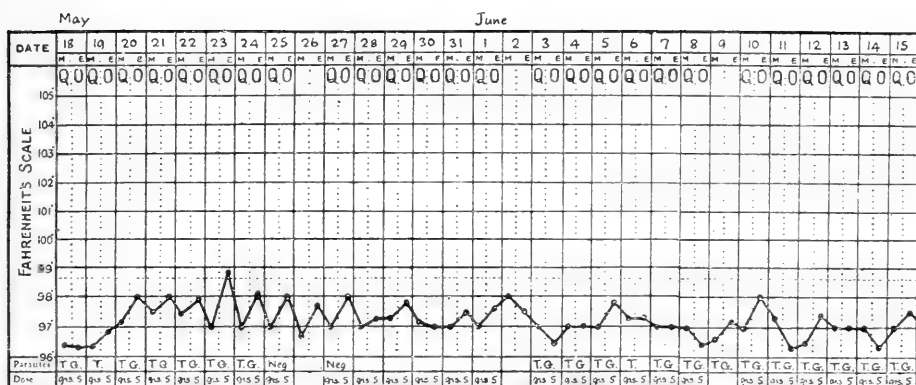
Given a total weekly dose of quinine, it is better as a palliative to divide it into two equal parts and administer one on each of two consecutive days, than to divide it into six equal parts and administer one on each of six consecutive days: in other words, as a palliative, *interrupted* is preferable to *continuous* quinine treatment in simple tertian malaria.

### REFERENCE

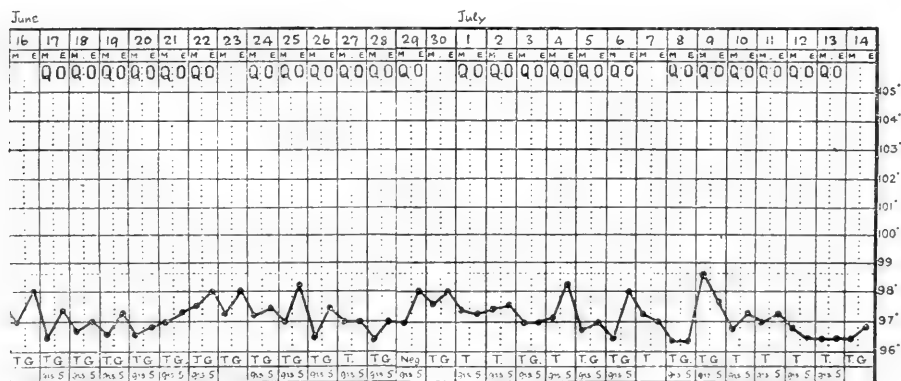
- STEPHENS, J. W. W., YORKE, W., BLACKLOCK, B., MACFIE, J. W. S., COOPER, C. F., and CARTER, H. F. (1918). Studies in the Treatment of Malaria: VIII. Oral Administration of Quinine Sulphate for two consecutive days weekly over prolonged periods, in Simple Tertian Malaria. *Ann. Trop. Med. & Parasitol.*, Vol. XI, pp. 331-358.



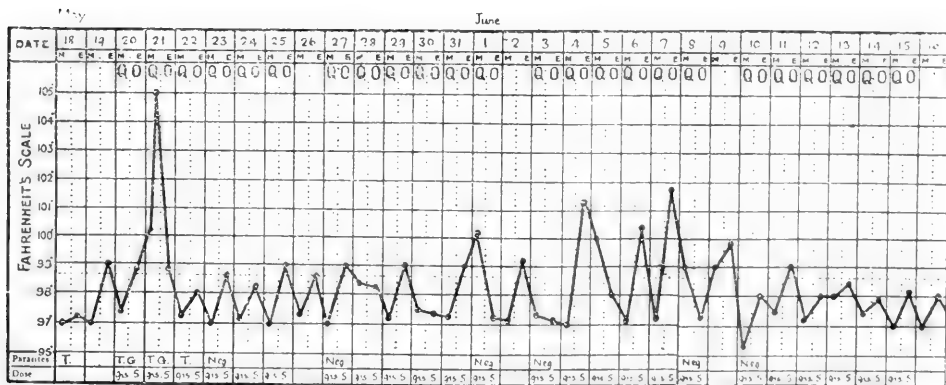
## CASE 946 (Part I)

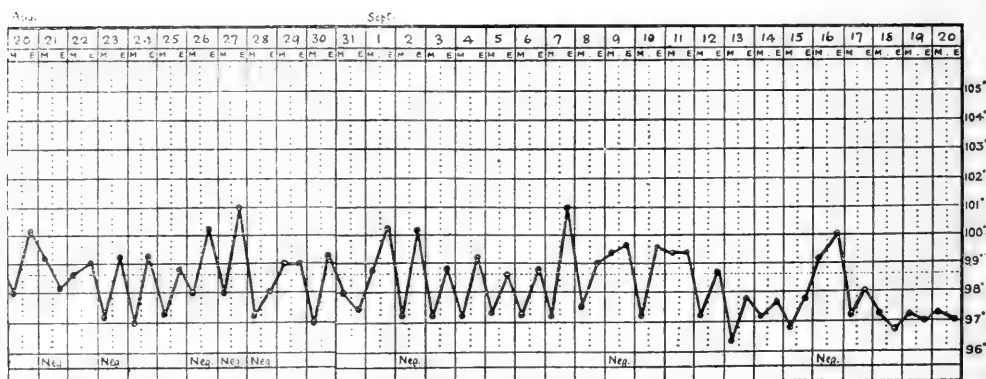
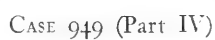
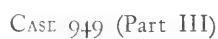


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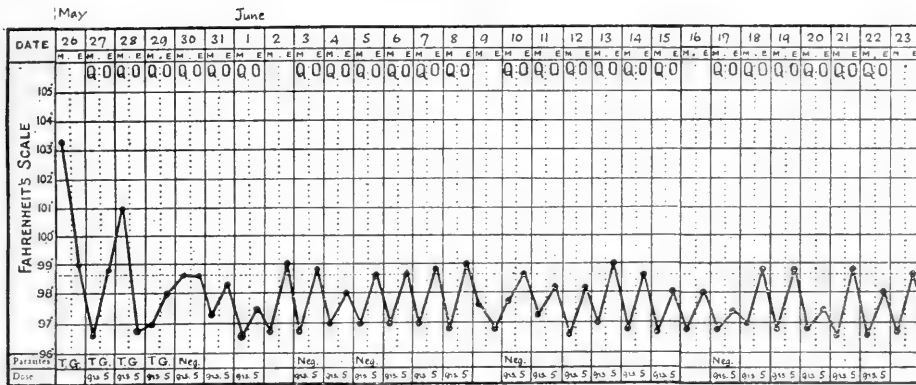


## CASE 949 (Part I)





## CASE 951 (Part I)



## CASE 951 (Part II)

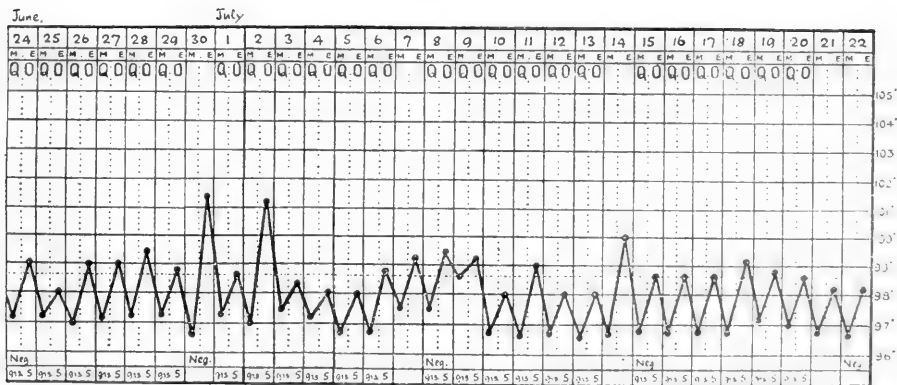










TABLE XI.

Results of oral administration of quinine sulphate in solution, grains 5, on each of six consecutive days weekly for 8 weeks.

† E.A. = East Africa. Eng. = England. It. = Italy. S. = Salonika.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse
								Week of Treatment										
								1st	2nd	3rd	4th	5th	6th	7th	8th			
923	S.	11	7	4	12.7.18	1	...	P†	4	1	1	1	3	2	0	1	...	
924	S.	9	6	5	12.7.18	3	...	P	P	2	1*	2	P	P	0	18-23	18	
925	S.	22	6	5	12.7.18	...	...	3	1	1	0	P	P	P	0	1-10	10	
926	It.	11	4	4	12.7.18	1	1	0	0	0	0	0	0	0	0	10-17	19	
927	S.	10	7	2	12.7.18	Apirexia	1	0	1*	0	0	0	1*	0	0	1-18	15	
928	S.	10	5	2	12.7.18	3	...	P	P	2	0	0	1*	1*	2*	1-18	18	
929	S.	31	7	2	14.7.18	2	...	1	3	P	P	P	P	1*	P	2-8	...	
930	S.	21	5	4	17.7.18	Apirexia	1	1*	P	1	0	0	1*	1*	0	...	...	
931	S.	25	6	6	17.7.18	2	3-5	0	0	0	0	0	P	P	0	1-6	6	
932	S.	16	5	4	16.7.18	Same day	2-5	0	0	1*	0	0	0	0	0	...	...	
933	S.	10	5	5	17.7.18	1	2-5	0	P	0	0	0	3	P	P	1-5	21	
934	E.A.	23	6	4	16.7.18	2	2-5	0	4	1	2	P	P	P	0	1-6	18	
935	S.	21	5	3	17.7.18	Same day	1-4	P	P	1	0	2	1*	0	0	1-4	4	
936	S.	11	6	5	19.7.18	2	3	0	2*	0	0	P	2	0	0	1-4	6	
937	E.A.	27	7	4	21.7.18	5	1-5	0	P	0	1	P	P	0	0	2-8	21	

101° F. on 25th, 102.8° F. on 26th days.

101° F. on 35th, 103.8°  
F. on 26th days.

† As in the subsequent weeks *only one* routine blood examination was made (at the end of each week), the letter 'P' in the first week of treatment indicates that parasites were present on the 7th day of treatment, and does not refer to parasitic records earlier in the week. Three days are allowed for the initial fever to subside. A numeral, e.g., '2', in the first week therefore indicates that there were two subsequent rises of temperature, both parasitic; these are recorded because in all weeks every rise of temperature was examined microscopically and the results recorded, in addition to those of the weekly examination.



TABLE XI—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period in days in cases in which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
938	S.	11	6	2	23.7.18	4	5	1	1	0	2*	0	0	P	0	28	26	...	
939	E.A.	6	6	4	22.7.18	1	4-5	0	0	0	P	0	0	0	P	1-3	3	...	
940	S.	11	5	3	18.7.18	3	4	0	0	0	P	0	0	0	1*	18	19	...	103° F. on 4th day.
941	S.	11	4	3	23.7.18	Same day	1	0	1	1	2	1*	0	0	0	1-2	1	...	
942	S.	38	7	7	3.8.18	1	3	0	P	1	0	0	1	1	0	1-8	8	...	
943	S.	10	4	4	28.7.18	1	...	P	1	1	P	0	2	0	0	1	6	...	103° F. on 16th day; 100° F. on 24th and 25th days; 105° F. on 48th day.
944	S.	10	8	3	5.8.18	2	2	0	0	0	0	0	0	0	0	...	...	79	
945	S.	18	7	6	6.8.18	1	4	P	3	3	2	2	3	4	3*	1-10	10	...	Parasites persist without fever for 60 days after cessation of treatment. <i>Vide</i> chart.
946	E.A.	9	8	4	13.7.18	Apirexia	...	P	0	P	P	P	P	P	P	1	...	...	
947	S.	11	7	2	21.7.18	Apirexia	1	0	0	0	0	0	0	0	0	...	...	74	
948	S.	10	5	5	16.7.18	2	3	0	0	0	0	0	1*	1*	1*	...	...	92	100° F. on 29th and 70th days.
949	S.	11	8	6	16.7.18	2	3	0	1*	4*	0	2*	2*	3*	3*	...	...	83	Irregular temperature after cessation of treatment. <i>Vide</i> chart.
950	S.				17.7.18	1	2	0	0	0	0	0	0	0	2*	6-10	9	...	100-8° F. on 7th day. <i>Vide</i> chart.
951	Eng.	2	...	...	20.7.18	2	3	0	0	0	0	0	1*	1*	1*	8-14	17	...	101° F. on 6th, 100° F. on 14th days.
952	Eng.	3	1	...	21.7.18	2	4	0	0	0	0	0	0	0	2*	16-21	20	...	

TABLE XI—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases in which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
953	S.	11	4	2	20.7.18	2	2	0	0	0	0	0	0	0	0	24-25	24	...	Quinine orally, grs. 45, on 61st day. Quinine intramuscularly grs. 15 × 2, in 7th week. Quinine intramuscularly grs. 15 × 2 in 5th week. <i>Vide</i> chart. Condition uncontrolled. Quinine intramuscularly grs. 15 × 2 in 3rd week. <i>Vide</i> chart. Condition uncontrolled; treatment changed. Condition uncontrolled; treatment changed. Condition uncontrolled; treatment changed. Condition uncontrolled; treatment changed.
954	S.	14	6	6	23.7.18	1	3	0	0	0	0	0	0	0	0	10-16	15	...	
955	S.	19	5	4	23.7.18	2	3	0	0	0	0	3*	0	0	0	7-13	13	...	
956	S.	7	9	8	22.7.18	4	4	0	0	0	0	0	P	0	0	...	...	116	
957	S.	10	9	2	20.7.18	1	2	0	0	0	0	3*	0	0	0	...	...	77	
958	S.	28	3	3	10.8.18	1	2	0	0	2*	0	0	0	0	0	...	...	66	
959	S.	15	5	3	10.8.18	1	...	P	3	P	P	0	0	1*	P	1	7	...	
960	S.	13	3	2	22.8.18	1	...	P	0	0	0	0	0	0	0	12-18	15	...	
961	S.	9	4	3	25.8.18	Same day	2	0	0	0	0	0	0	0	0	53-58	...	...	
962	S.	26	5	4	13.7.18	3	1	0	P	1	0	P	P	P	...	...	...	...	
963	S.	6	3	2	25.8.18	3	4	0	0	0	3	2	...	...	...	...	...	...	
964	S.	10	5	4	25.6.18	2	...	P	3	1	0	5	...	...	...	...	...	...	
965	S.	23	8	3	10.8.18	2	2	0	0	4	...	...	...	...	...	...	...	...	
966	S.	22	6	1	4.6.18	4	1-5	0	2*	3	...	...	...	...	...	...	...	...	
967	S.	9	3	3	27.5.18	...	...	4	3	...	...	...	...	...	...	...	...	...	
968	...	...	...	...	6.6.18	3	...	P	3	...	...	...	...	...	...	...	...	...	
969	S.	12	9	1	3.6.18	...	...	3	2	...	...	...	...	...	...	...	...	...	

TABLE XII.

Results of oral administration of quinine sulphate in solution, grains 15, on each of two consecutive days weekly for 8 weeks.

† E.A. = East Africa. F. = France. M. = Mesopotamia. S. = Salonika.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
970	S.	10	4	3	19.6.18	1	2	0	0	0	0	0	0	0	...	...	117	101.8° F. on 12th, 102.4° F. on 13th, 100.8° F. on 18th days (influenza).	
971	S.	10	5	4	19.6.18	Apyrexia	2	0	0	1*	0	0	P	6	1	1	...		
972	E.A.	9	5	3	19.6.18	1	3	0	0	1*	0	0	0	0	13-18	15	...		
973	S.	10	5	5	19.6.18	Same day	1	0	2*	0	0	0	0	0	...	...	...	Not observed after treatment.	
974	S.	11	4	3	19.6.18	Same day	1	1*	0	0	0	0	0	0	11	10	...		
975	S.	6	4	3	19.6.18	Apyrexia	2	0	0	0	0	0	0	2	1-4	4	...		
976	S.	14	5	4	19.6.18	3	3	0	0	0	0	0	0	0	34-38	37	...		
977	S.	10	...	5	19.6.18	1	2	1*	0	0	0	0	0	1*	27-31	30	...	100° F. on 5th and 8th days; 102° F. on 11th, 101° F. on 19th, 100° F. on 26th days.	
978	S.	21	4	3	19.6.18	1	2	1*	0	0	0	0	0	0	13	16	...		
979	E.A.	11	5	3	19.6.18	Apyrexia	3	0	1*	1*	0	0	0	P	6-12	11	...		
980	E.A.	22	6	3	19.6.18	5	3	0	P	4	2	2	P	1	1	1	...	vide chart.	
981	E.A.	11	5	3	19.6.18	Apyrexia	1	0	0	0	0	0	0	0	1-5	...	...	No febrile relapse in 106 days.	
982	E.A.	8	6	3	19.6.18	2	2	0	0	0	0	0	0	0	1-5	9	...		
983	S.	12	4	2	19.6.18	1	3	0	0	0	0	0	0	0	13-16	15	...	102° F. on 8th day.	
984	E.A.	8	4	3	19.6.18	3	3	0	1	1	0	1	0	0	1-3	3	...		

TABLE XII continued

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
985	S.	26	5	5	19.6.18	1	2	0	0	0	0	0	0	1	P	6-11	10	...	
986	S.	12	4	4	19.6.18	5	2	0	0	0	0	0	0	0	0	55-56	56	...	
987	E.A.	9	6	3	26.6.18	3	2	0	0	1	0	0	0	0	0	20-23	22	...	
988	S.	12	4	3	19.6.18	Apyrexia	1	0	0	0	0	0	0	0	0	8-12	11	...	
989	S.	10	3	3	19.6.18	1	3	1*	0	1*	1*	0	0	0	0	...	...	110	
990	S.	9	4	3	19.6.18	1	1	0	0	1*	0	0	0	0	2	1	1	...	
991	S.	24	4	3	19.6.18	1	1	0	0	0	0	0	0	0	0	...	...	78	
992	S.	11	3	3	19.6.18	1	2	0	0	1*	0	0	0	0	0	13-14	13	...	
993	E.A.	18	5	3	19.6.18	1	2	0	0	0	0	0	0	0	0	6-12	42	...	
994	E.A.	7	6	3	19.6.18	1	4	0	0	0	0	0	P	P	P	1	12	...	
995	F.	4	2	2	26.6.18	Same day	2	0	0	0	0	0	0	0	0	13-16	13	...	
996	S.	12	5	4	26.6.18	Same day	1	0	0	0	0	0	0	2	0	1	18	...	
997	M.	13	11	7	26.6.18	Apyrexia	1	0	0	2	0	0	0	0	0	...	...	62	No febrile relapse in 98 days.
998	E.A.	23	8	3	26.6.18	Apyrexia	1	0	0	0	0	0	0	0	0	13-19	...	...	No febrile relapse in 108 days.
999	E.A.	12	6	3	26.6.18	Apyrexia	4	0	0	0	0	0	0	0	0	34-40	...	...	
1000	E.A.	7	6	4	3.7.18	Apyrexia	1	0	0	0	0	0	0	0	0	...	...	64	
1001	S.	10	5	4	3.7.18	1	4	0	0	0	P	P	P	0	0	13-19	...	...	No febrile relapse in 76 days.
1002	S.	23	7	-6	3.7.18	1	2	0	0	1*	0	0	0	0	0	...	...	42	

TABLE XII—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period in days in cases in which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1003	S.	11	4	3	13.6.18	1	1-3	o	o	o	o	o	o	o	o	16	...	...	No febrile relapse in 63 days.
1004	S.	23	5	4	13.6.18	2	1-3	o	1*	o	2	o	o	1	1	8	...	...	No febrile relapse in 84 days.
1005	S.	21	5	4	27.6.18	Same day	No record	o	1	2	o	o	1	1	o	11	7	...	Irregular temperature after cessation of treatment. Almost daily non-parasitic rises.
1006	S.	23	5	4	27.6.18	1	1-7	o	o	o	o	1*	o	1*	3*	...	...	68	Pneumonia on 3rd day after cessation of treatment.
1007	S.	13	5	4	27.6.18	1	2-7	o	o	2	P	o	o	o	o	6-11	28	...	Not observed after treatment.
1008	S.	11	...	...	27.6.18	1	2-7	o	o	o	o	o	o	o	o	9	...	...	100° F. on 25th and 29th days.
1009	E.A.	24	4	3	27.6.18	1	1-7	o	o	o	P	o	o	1*	o	10	16	...	
1010	S.	7	4	3	27.6.18	1	1-7	o	o	o	o	o	o	o	o	9	12	...	
1011	S.	12	...	...	27.18	1	1-6	o	o	o	o	o	o	o	o	...	...	...	
1012	E.A.	9	4	3	27.6.18	1	1	o	o	o	1*	o	1	o	o	1	1	...	
1013	S.	21	6	5	27.6.18	2	4-6	o	3	3	P	P	o	o	o	14-20	29	...	
1014	S.	21	5	5	27.6.18	1	3-6	o	o	o	o	P	1	o	o	9	24	...	
1015	S.	10	10	9	27.6.18	2	1-4	o	o	2	1	o	1*	o	o	35	35	...	
1016	S.	12	4	3	27.6.18	1	1-4	o	o	o	o	o	1*	o	1*	41-42	42	...	
1017	S.	23	4	3	27.6.18	1	1-4	o	o	o	1*	o	o	o	o	12	9	...	
1018	S.	26	4	3	27.6.18	2	2	o	o	o	o	o	o	o	o	13-18	18	...	

TABLE XII. *continued.*

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases in which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1019	S.	7	4	3	27.6.18	1	2-4	0	0	0	0	0	0	0	13-19	21	...	102° F. on 53rd, 104° F. on 54th and 55th days: probably rheumatic.	
1020	S.	13	3	2	27.6.18	1	1-3	0	0	0	0	0	0	0	41-47	55	...		
1021	S.	11	4	3	27.6.18	1	2-3	0	0	0	0	0	0	1*	13-19	26	...		
1022	S.	10	4	3	27.6.18	1	2-3	0	0	0	0	0	0	1*	...	...	68		
1023	S.	12	4	4	27.6.18	1	1-2	0	0	0	0	0	1*	0	...	...	69	100° F. on 8th and 10th days; 102° F. on 13th, 101° F. on 15th days. No febrile relapse in 69 days. Not observed after treatment.	
1024	M.	26	25	24	4.7.18	...	1	5*	2*	3*	2*	2*	1*	1*	...	...	63		
1025	S.	22	6	5	4.7.18	1	1-7	0	0	3	0	0	P	0	12-18	18	...		
1026	S.	23	5	4	4.7.18	1	1	0	0	0	0	1*	1*	1*	13-14	14	...		
1027	S.	22	4	4	4.7.18	Same day	1-7	0	0	0	0	0	0	0	...	...	50	103° F. on 26th day.	
1028	...	...	...	...	4.7.18	Same day	1-7	0	0	0	0	0	0	0	13-19	...	...		
1029	S.	21	6	6	4.7.18	2	3	1*	0	2	P	1	0	3	1	...	...		
1030	S.	25	5	4	4.7.18	1	1-6	0	1*	3*	2*	0	1	1*	13-14	14	...		
1031	S.	11	6	5	4.7.18	1	1-7	0	0	0	0	1	1	2*	27-33	47	...		
1032	S.	15	10	2	4.7.18	1	1	0	0	0	0	0	0	0	...	...	62		
1033	S.	13	4	4	11.7.18	1	1	0	0	0	0	0	0	0	...	...	54		
1034	S.	10	4	4	11.7.18	1	1-7	0	0	3	0	1	1	P	6-9	9	...		

TABLE XIII.

Results of oral administration of quinine sulphate in solution, grains 15, on each of six consecutive days, weekly for 8 weeks.

† E.A. = East Africa. S. = Solomon.

Number of case	† Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1035	S.	9	4	3	13.7.18	2	3	0	0	0	0	0	0	4	P	11-15	16	...	Quinine intramuscularly 15 × 2 in 8th week.
1036	S.	16	4	3	13.7.18	Apyrexia	2	0	0	0	0	0	0	0	P	40-44	45	...	
1037	E.A.	16	7	4	13.7.18	2	3	0	0	0	0	0	0	0	1*	9-13	11	...	
1038	S.	16	5	4	15.7.18	1	3	0	0	1*	1	P	1*	0	0	8-12	11	...	<i>Vide</i> chart.
1039	...	...	...	...	15.7.18	4	1	0	0	0	0	0	0	0	0	...	...	85	
1040	S.	10	5	5	17.7.18	2	2	0	0	0	0	0	0	1*	0	...	...	...	Not observed after treatment.
1041	S.	10	7	2	18.7.18	Apyrexia	3	0	0	0	1*	0	0	0	0	6-12	14	...	
1042	S.	25	6	5	19.7.18	1	1	0	0	0	0	0	0	0	0	...	...	95	
1043	S.	5	5	2	22.7.18	3	2	1*	0	0	0	0	0	0	0	...	...	77	
1044	S.	12	3	2	23.7.18	1	1	0	0	0	0	0	0	0	0	7-13	12	...	
1045	S.	22	5	4	23.7.18	Apyrexia	1	0	0	0	0	0	0	0	0	7-13	14	...	
1046	S.	20	6	5	1.8.18	1	1	0	0	0	0	0	0	0	0	1	1	...	100° F. on 6th, 13th, 26th, 37th, 38th, and 66th days.
1047	S.	10	3	2	9.8.18	1	2	0	0	0	0	0	0	0	0	...	...	77	
1048	S.	12	4	2	14.8.18	1	2	0	0	0	0	0	0	0	0	...	...	70	
1049	S.	12	2	1	15.8.18	1	3	0	0	2*	0	0	0	0	0	...	...	86	
1050	S.	19	5	4	12.7.18	1	1-2	0	0	0	0	2	1*	0	0	39-45	45	...	100° F. on 14th day.

TABLE XIII—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1051	S.	8	5	4	12.7.18	1	1-2	0	0	0	1*	0	0	0	0	...	...	73	100° F. on 2nd, 14th, 23rd and 28th days.
1052	S.	20	6	5	12.7.18	1	1-2	0	0	0	0	0	0	0	0	...	...	63	
1053	S.	31	6	5	12.7.18	2	3-7	0	0	0	0	0	2*	0	0	3-10	11	...	100° F. on 1st day.
1054	S.	13	9	6	12.7.18	2	2	0	1*	0	1*	0	1*	1*	0	...	...	63	102.4° F. on 15th, 17th and 25th days.
1055	E.A.	21	7	4	12.7.18	Apyrexia	1-2	0	0	0	0	1*	0	0	0	...	...	80	101° F. on 6th day.
1056	S.	22	5	4	12.7.18	2	2-7	0	0	0	0	0	0	0	0	...	...	63	
1057	S.	11	5	4	13.7.18	2	2-7	0	0	0	0	1*	2*	0	1*	17	17	...	100° F. on 7th and 14th days.
1058	E.A.	26	10	8	15.7.18	2	2-6	0	1*	1*	0	0	0	1*	0	8-10	10	...	
1059	S.	13	6	5	15.7.18	2	1	0	0	0	0	0	0	1*	0	8-11	11	...	
1060	E.A.	11	9	4	15.7.18	1	2	0	0	0	0	0	0	0	0	1-6	7	...	
1061	S.	28	5	5	15.7.18	3	2-5	0	0	0	0	0	0	0	0	9-15	14	...	
1062	E.A.	9	7	4	16.7.18	2	2-5	0	0	0	0	0	0	0	0	1-6	19	...	
1063	S.	23	5	4	17.7.18	Same day	1-4	0	0	0	0	0	0	0	0	24-26	26	...	100° F. on 6th day.
1064	S.	11	7	4	15.7.18	1	1-4	0	0	5	1	0	3	0	1	1-3	14	...	
1065	S.	13	7	4	17.7.18	2	2-4	0	0	0	0	0	1*	0	0	11-18	19	...	
1066	S.	11	8	2	18.7.18	Same day	2	2*	0	0	0	0	0	0	0	11-18	19	...	
1067	S.	11	4	3	19.7.18	2	1-3	0	0	0	1*	1	1*	1*	0	10-12	12	...	
1068	S.	13	5	3	19.7.18	1	1-3	0	1*	0	0	0	0	0	0	10-12	13	...	



TABLE XIII—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases in which did not relapse	Remarks	
								Week of Treatment												
								1st	2nd	3rd	4th	5th	6th	7th	8th					
1069	S.	13	6	6	19.7.18	1	1-3	o	o	o	o	o	o	o	o	o	69	...	...	100° F. on 40th and 43rd days.
1070	S.	21	5	4	19.7.18	Apyrexia	1-4	o	o	o	1*	o	o	o	o	o	...	...	11	...
1071	S.	13	6	5	19.7.18	Same day	1-3	o	o	o	o	o	o	o	o	o	...	42	44	...
1072	S.	14	5	4	18.7.18	2	3	o	o	o	o	o	o	o	o	o	...	...	...	158
1073	S.	28	24	3	21.7.18	1	1-7	o	o	o	o	o	o	o	o	o	...	8	2-8	...
1074	S.	12	9	6	21.7.18	2	1-7	o	o	o	o	o	o	o	o	o	...	...	16-22	...
1075	S.	8	4	4	22.7.18	3	2	o	o	o	o	o	o	o	o	o	...	13	7-14	...
1076	S.	12	3	3	22.7.18	1	2	o	o	o	o	o	o	o	o	o	...	...	...	...
1077	S.	11	5	4	25.7.18	1	1-4	o	o	o	o	o	o	o	o	o	...	...	...	Not observed after treatment. 101.4° F. on 22nd, 100.4° F. on 24th, 100.8° F. on 30th, 100° F. on 31st days, 100° F. on 6th, 104° F. on 10th days.
1078	S.	22	6	5	18.7.18	2	1-6	o	o	o	o	o	o	o	o	o	...	...	...	...
1079	S.	11	5	4	22.7.18	1	3	o	1*	o	o	o	o	o	o	o	...	22	14-20	...
1080	S.	21	6	2	25.7.18	1	3	o	1*	o	o	o	o	o	o	o	...	...	...	110
1081	S.	12	5	5	25.7.18	1	3	1	3	1	2	o	o	o	o	o	...	17	12-17	...
1082	S.	12	7	3	3.8.18	2	3-7	o	o	o	o	o	o	o	o	o	...	...	...	64
1083	S.	0	2	1	13.8.18	1	2	o	o	2	P	1	2	...	...	...	...	...	...	Quinine intramuscularly grs. 15 × 2 in 7th week.

TABLE XIV.

Results of oral administration of quinine sulphate in solution, grains 45, on each of two consecutive days weekly for 8 weeks.

† E.A. = East Africa.

S. = Salomka.

Number of case	† Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases in which did not relapse	Remarks	
								Week of Treatment												
								1st	2nd	3rd	4th	5th	6th	7th	8th					
1084	E.A.	9	4	3	8.6.18	2	3	○	○	1*	○	1	○	○	○	○	6-12	18	...	
1085	E.A.	7	5	3	8.6.18	1	2	○	○	○	○	○	○	○	○	○	1-5	9	...	
1086	E.A.	9	6	3	8.6.18	2	2	○	○	○	○	○	○	○	○	○	13-17	17	...	
1087	E.A.	12	6	4	8.6.18	2	3	○	1*	○	○	P	P	5*	1*	13	14	...	Febrile attacks in 7th and 8th weeks due to influenza and sciatica. 100° F. on 4th and 8th days after cessation of treatment. <i>Vide</i> chart. Quinine orally on 19th day.	
1088	E.A.	11	6	4	8.6.18	Apirexia	3	○	○	○	○	○	○	1*	○	○	6-12	...	...	
1089	S.	12	4	3	8.6.18	1	3	○	○	○	○	○	○	○	○	○	6-12	12	...	
1090	E.A.	13	7	4	7.6.18	2	2	○	○	○	○	○	○	1	1	1	16-17	15	...	
1091	E.A.	10	6	3	8.6.18	Same day	2	○	○	○	○	○	○	○	○	○	...	...	60	Relapsed parasitically in 62-68 days and febrilely in 68 days.
1092	S.	23	4	3	8.6.18	Apirexia	1	○	○	1*	○	○	○	○	○	○	6-12	13	...	102-4° F. on 26th day.
1093	S.	10	4	3	8.6.18	1	2	○	1*	○	○	○	○	○	○	○	...	...	77	
1094	S.	8	4	3	8.6.18	1	1	○	○	○	○	○	○	○	○	○	13-18	18	...	
1095	E.A.	11	4	3	8.6.18	Apirexia	2	○	○	○	○	○	○	○	○	○	20-26	26	...	
1096	E.A.	17	4	3	8.6.18	1	1	○	○	○	○	○	○	○	○	○	13-19	17	...	
1097	E.A.	25	4	3	8.6.18	Apirexia	1	○	○	2*	○	○	○	○	○	○	13-19	23	...	

TABLE XIV—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases in which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1098	E.A.	7	5	3	8.6.18	Apirexia	2	0	0	2	0	0	0	0	0	12-18	18	...	101° F. on 9th, 101.5° F. on 10th days.
1099	S.	10	5	4	15.6.18	Same day	2	0	0	0	0	0	0	0	0	...	...	69	
1100	S.	11	5	5	15.6.18	Apirexia	2	0	0	0	1*	0	0	0	0	5-12	13	...	
1101	S.	25	4	2	15.6.18	Same day	2	0	0	0	0	0	0	0	0	14	...	...	Discharged on 16th day.
1102	E.A.	10	5	5	15.6.18	2	2	0	0	0	0	0	0	0	0	8-12	18	...	
1103	S.	23	6	5	15.6.18	1	2	0	0	0	0	0	0	0	2*	...	...	83	101.8° F. on 64th day.
1104	S.	12	4	3	15.6.18	1	2	0	0	0	0	0	0	0	0	13-17	16	...	
1105	E.A.	7	5	3	15.6.18	Apirexia	2	1*	0	0	0	0	0	0	0	13-19	18	...	Not observed after treatment.
1106	S.	13	...	...	27.7.18	1	1	0	0	0	0	0	0	0	0	...	...	...	Not observed after treatment.
1107	S.	12	4	3	6.7.18	1	2	0	0	0	0	0	0	0	0	...	...	100	
1108	E.A.	12	5	5	27.7.18	1	2	0	0	0	0	0	0	0	0	...	...	...	Not observed after treatment.
1109	S.	19	6	5	27.7.18	1	4	0	2*	0	0	0	0	0	1*	...	...	...	Not observed after treatment.
1110	S.	13	7	5	19.5.18	1	1	0	0	0	0	0	0	0	0	12	16	...	
1111	E.A.	25	5	2	25.5.18	2	2	0	0	0	0	0	0	0	0	...	...	74	
1112	E.A.	17	4	2	25.5.18	Apirexia	1	[cr.]	[cr.]	[cr.]	[cr.]	0	0	0	0	6-8	7	...	
1113	E.A.	5	5	2	25.5.18	2	2	0	0	0	0	0	0	0	0	6-9	9	...	
1114	E.A.	11	5	2	25.5.18	1	2	0	0	0	0	0	0	0	0	12	10	...	

TABLE XIV continued.

Number of case	Place of infection	Interval (in months) between admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1115	E.A.	11	5	2	25.5.18	Apyrexia	1	0	0	0	0	0	0	0	0	...	...	31	
1116	E.A.	6	4	2	25.5.18	2	2	0	0	0	0	0	0	0	0	6-12	13	...	
1117	S.	20	3	3	25.5.18	1	2	[Gr.]	0	0	1*	0	0	0	0	11-12	9	...	
1118	E.A.	9	4	2	25.5.18	1	2	0	0	0	0	0	0	0	0	6-12	13	...	
1119	E.A.	16	3	2	25.5.18	1	1	0	0	0	0	0	0	1*	0	20-26	26	...	100° F. on 20th day.
1120	E.A.	8	4	2	25.5.18	1	2	0	0	2*	0	0	0	0	0	6-12	14	...	
1121	E.A.	11	4	2	25.5.18	Same day	2	0	0	0	2*	0	0	0	0	13-19	18	...	
1122	E.A.	10	5	2	25.5.18	2	3	0	0	0	0	1*	0	0	0	13-19	18	...	
1123	E.A.	6	6	3	1.6.18	4	1	0	0	0	P	1*	0	0	0	13-19	18	...	
1124	S.	21	5	4	1.6.18	1	2	0	0	0	0	0	0	0	0	6-12	16	...	
1125	S.	24	5	4	1.6.18	1	1	0	0	0	0	0	0	0	0	6-12	27	...	
1126	S.	22	5	5	1.6.18	Apyrexia	2	0	0	0	0	0	0	0	0	...	...	68	Influenza on 33rd and 34th days after cessation of treatment.
1127	S.	11	5	4	1.6.18	1	1	0	0	0	0	0	0	0	0	14-20	21	...	
1128	E.A.	11	5	3	1.6.18	1	2	0	1*	0	0	0	0	0	0	6-12	15	...	
1129	E.A.	10	5	3	1.6.18	1	2	0	0	0	0	0	0	0	0	13-21	26	...	
1130	E.A.	13	5	3	1.6.18	Apyrexia	2	0	0	0	0	0	0	0	0	41-47	48	...	
1131	E.A.	8	6	3	1.6.18	2	3*	0	0	0	0	0	0	0	0	27-43	35	...	

TABLE XIV—continued.

Number of case	#Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment		Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
		Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment						Week of Treatment											
1st	2nd	3rd	4th	5th	6th	7th	8th													
1132	E.A.	15	4	3	8.6.18	1	1	1	0	0	0	1*	0	0	0	13-19	20	...	Febrile attacks in 3rd week due to influenza.	
1133	E.A.	12	6	3	8.6.18	1	2	0	0	0	0	0	0	0	0	31	29	...		
1134	E.A.	6	4	3	8.6.18	1	2	0	0	2*	0	0	0	0	0	13-18	17	...		
1135	E.A.	10	4	3	8.6.18	Same day	3	0	0	0	0	0	0	0	0	1-3	3	...		
1136	S.	24	6	6	18.7.18	Same day	2	2	0	0	0	0	0	0	0	14	14	...	Measles on 12th day after cessation of treatment.	
1137	...	...	...	...	18.7.18	2	1-5	0	0	0	0	0	0	0	1*	14-20	20	...		
1138	S.	15	5	4	25.7.18	Same day	1-4	1-4	0	0	0	1*	2*	0	1*	15-17	16	...		
1139	S.	26	5	5	25.7.18	2	3-4	1*	0	0	0	0	0	0	0	7-12	12	...		
1140	S.	25	4	4	25.7.18	1	1-7	0	0	0	0	0	0	0	0	1-8	8	...		
1141	S.	13	6	5	25.7.18	1	1-5	0	0	1*	0	0	0	0	0	...	...	40	...	
1142	S.	17	7	3	25.7.18	Same day	1-2	1-2	0	0	0	0	0	0	0	15-16	17	...		
1143	S.	12	6	6	25.7.18	1	1-3	1-3	0	1*	0	1*	2*	1*	2*	7-9	7	...		
1144	S.	18	5	4	25.7.18	2	1-2	1-2	1*	0	2	2*	0	2*	0	...	...	54		
1145	E.A.	27	13	12	1.8.18	Apyrexia	1-2	1-2	0	0	0	0	0	0	0	8-10	10	...	...	
1146	...	...	...	...	25.7.18	2	2-3	2-3	0	0	1	2	3	1	0	10	10	...		
1147	S.	12	6	5	25.7.18	3	2	2	0	0	1*	0	0	0	2*	7-12	12	...		
1148	E.A.	27	7	4	25.7.18	2	1-2	1-2	0	0	0	0	0	0	0	7-13	14	...		

TABLE XIV—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1149	E.A.	19	9	7	25.7.18	1	2	0	0	2	0	0	0	0	0	14	...	...	Low, intermittent temperature throughout. 102° F. on 6th, 104° F. on 20th, 102° F. on 45th, 100° F. on 55th days. 102° F. on 10th, 100° F. on 16th, 25th and 32nd days.  101° F. on 9th, 100° F. on 11th, 13th and 16th days, 102° F. on 24th day.
1150	E.A.	9	3	2	25.7.18	1	1	0	0	0	0	0	0	0	18	...	...		
1151	E.A.	18	10	7	25.7.18	1	1-5	0	0	0	0	0	0	0	14	...	...		
1152	S.	23	5	4	25.7.18	1	1-7	0	0	1* 2*	0	1*	0	0	...	...	76		
1153	S.	12	7	5	25.7.18	1	1-6	0	0	0	0	1* 1*	1*	1*	...	...	93		
1154	S.	23	5	4	25.7.18	Apixia	1	0	0	0	0	1*	0	0	...	...	71		
1155	S.	16	5	4	25.7.18	Same day	1-5	0	0	0	0	0	2	0	23	...	...		
1156	S.	24	8	7	1.8.18	1	1-4	0	0	0	0	0	0	0	15	...	...		
1157	S.	22	5	2	25.7.18	1	1	0	0	0	0	1* 1*	1* 1*	...	...	77			

# STUDIES IN THE TREATMENT OF MALARIA

## XIX. INTRAVENOUS INJECTIONS OF DISODO- LUARGOL IN SIMPLE TERTIAN MALARIA

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*(Received for publication 1 July, 1918)*

This drug, which is a neutral salt of silver, arsenic and antimony, was injected intravenously in thirteen cases. Two injections were given in four cases (1158-1161); 0·1 gramme on the first day and 0·15 gramme on the fifth day of treatment; and a single injection of 0·2 gramme in nine cases (1162-1170). All the cases were adult males infected either in Macedonia or in Egypt. In every instance a diagnosis of simple tertian malaria was made microscopically, and in all cases parasites were present in the blood on the day treatment was commenced. Blood examinations were made daily.

The results are summarised in Tables II and IV, which also contain the following additional information:—Place of infection and interval in months between present treatment and (a) first admission to a hospital with malaria, (b) leaving infected area, (c) arrival in England.

TABLE I.

Parasitic records after two small intravenous injections (0.1 gm. and 0.15 gm.) of Disodo-luargol in simple tertian malaria.

Number of case	Day of first injection 0.1 gm.	1st day after	2nd day after	3rd day after	Day of second injection 0.15 gm.	1st day after	2nd day after	3rd day after	4th day after	5th day after	6th day after	7th day after
1158	T.G.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	G.
1159	T.G.	T.	Neg.	Neg.	Neg.	Neg.	T.	Neg.	T.G.	T.G.	T.	T.
1160	T.G.	T.	T.	T.G.	T.G.	T.	G.	Neg.	Neg.	T.	T.G.	T.G.
1161	T.G.	G.	G.	T.G.	Neg.	T.	Neg.	Neg.	Neg.	G.	T.G.	G.

TABLE II.

Summary of TABLE I.

\* S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first injection	Parasites disappeared from cutaneous blood in — days after first injection	Parasitic relapse occurred in — days after last injection	Febrile relapse (above 100° F.) occurred in — days after last injection
1158	S.	15	4	2	24.5.18	Apyrexia	1	7	...
1159	S.	21	3	1	24.5.18	Apyrexia	2	2	...
1160	S.	6	1	0	24.5.18	7	7	5	8
1161	S.	10	3	2	24.5.18	3	4	1	7



TABLE III.

Parasitic records after a single larger intravenous injection (0.2 gm.) of Disodo-luargol in simple tertian malaria.

No. of case	Day of injection 0.2 gm	1st day after	2nd day after	3rd day after	4th day after	5th day after	6th day after	7th day after	8th day after	9th day after	10th day after	11th day after	12th day after	13th day after	14th day after	15th day after	16th day after	17th day after
1162	T.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	G.	Neg.	T.
1163	T.G.	T.G.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	G.	Neg.	T.G.	T.G.	T.G.	...	...	...	...
1164	G.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	T.	G.	Neg.	T.G.	...	...
1165	T.G.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	G.
1166	T.G.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	T.
1167	T.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	G.	G.	T.G.	...	...	...
1168	T.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	T.	Neg.	Neg.	T.G.	...	...	...	...	...
1169	T.G.	T.G.	T.G.	Neg.	Neg.	Neg.	Neg.	T.G.	G.	G.	G.	T.G.	T.G.	...	...	...	...	...
1170	T.G.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	G.	Neg.	G.	...	...	...	...

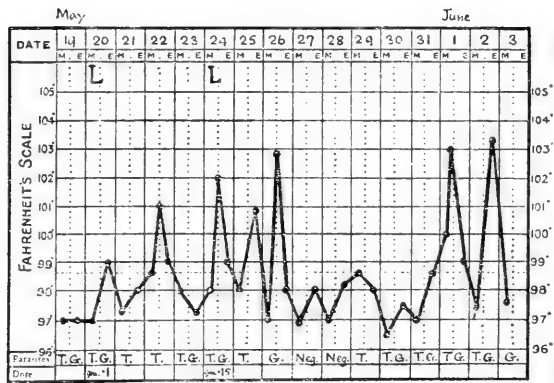
TABLE IV.

Summary of TABLE III.

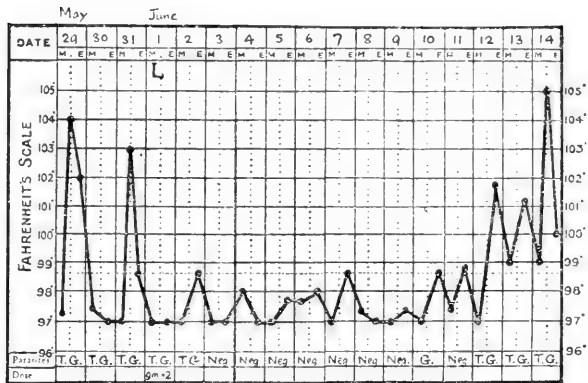
\* E. = Egypt. S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of treatment	Temperature fell to normal in — days after injection	Parasites disappeared from cutaneous blood in — days after injection	Parasitic relapse occurred in — days after injection	Febrile relapse (above 100° F.) occurred in — days after injection	Remarks
1162	S.	24	5	4	1.6.18	Apyrexia	1	15	18	
1163	S.	20	3	3	1.6.18	Same day	2	9	11	
1164	E.	30	5	2	1.6.18	1	1	12	14	
1165	S.	9	5	4	1.6.18	Same day	1	17	12	
1166	S.	22	5	3	1.6.18	1	1	17	18	
1167	S.	16	5	3	1.6.18	Apyrexia	1	12	12	
1168	S.	22	4	2	1.6.18	Apyrexia	1	9	12	
1169	S.	7	2	1	1.6.18	2	3	7	12	
1170	S.	11	4	3	1.6.18	Same day	1	11	7	

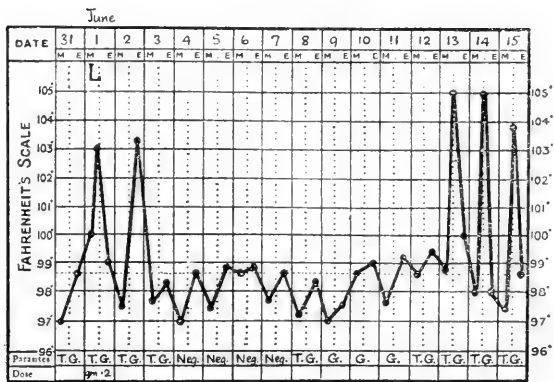
## CASE 1160



## CASE 1163



## CASE 1169



In the tables and charts :—

T. = simple tertian trophozoites or schizonts.

G. = simple tertian gametes.

Neg. = no parasites found.

L. = intravenous injection of luargol.

Tables I and II show that the two small injections (0·1 and 0·15 gramme respectively) had but little effect on the parasites or the temperature (Chart 1160).

Tables III and IV show that a single injection of a larger dose (0·2 gramme) caused the disappearance of the parasites from the peripheral blood in one to three days and that the temperature fell to normal within two days.\*

Parasitic relapses occurred in seven to seventeen days and febrile relapses in seven to eighteen days (Charts 1163 and 1169).

#### *Tolerance of treatment*

With the doses used no ill-effects were produced.

### SUMMARY

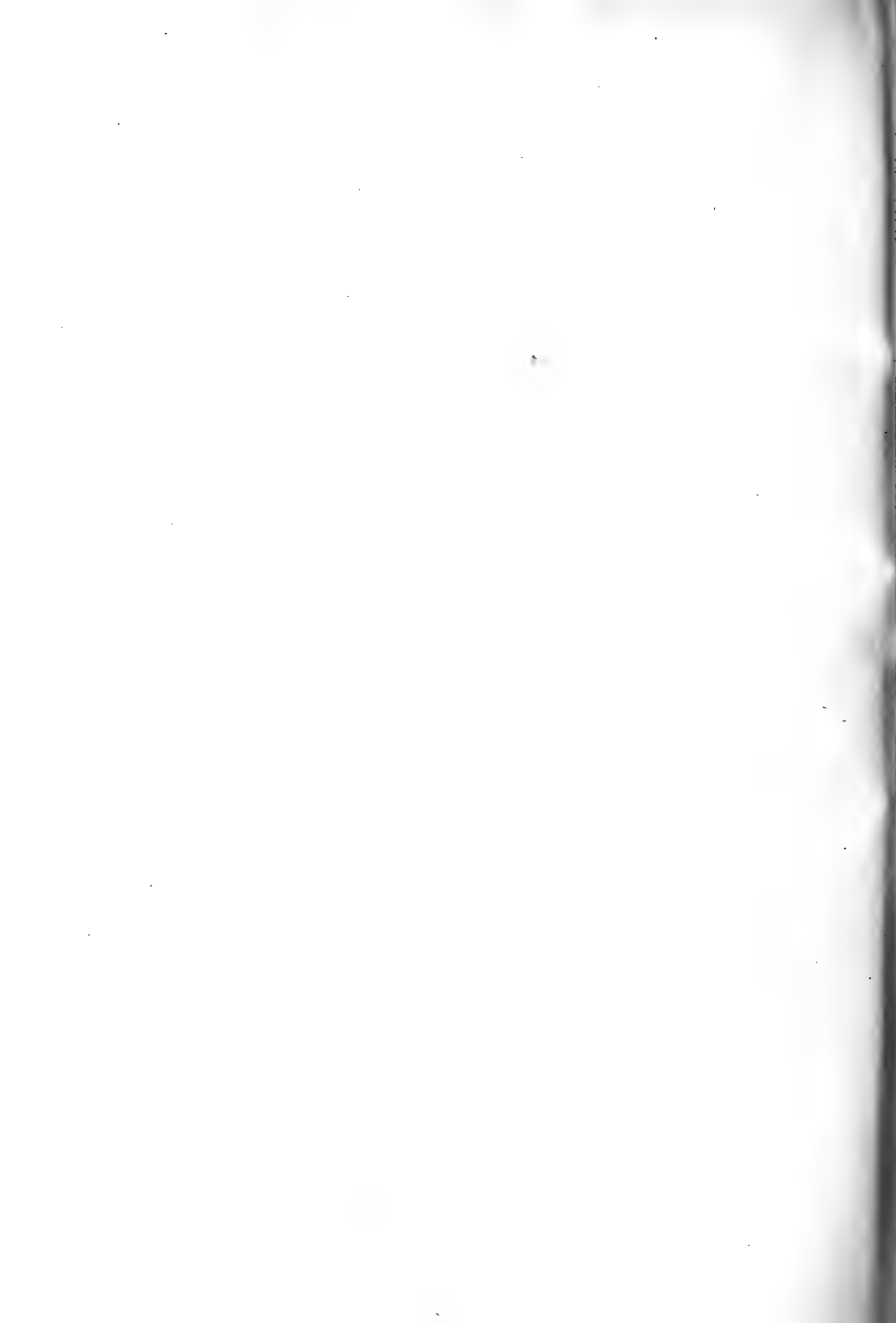
A single intravenous injection of 0·2 gramme of disodo-luargol caused a temporary disappearance of parasites from the cutaneous blood and controlled the symptoms. In all cases a relapse occurred within three weeks. Smaller doses were ineffective.

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\* By this is meant that the temperature fell to normal and remained so for at least two days.



# STUDIES IN THE TREATMENT OF MALARIA

## XX. INTRAMUSCULAR INJECTIONS OF COLLOSOL MANGANESE IN SIMPLE TERTIAN MALARIA

BY

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*Undertaken at the request of the War Office*

*(Received for publication 5 October, 1918)*

This preparation, supplied to us by the Crookes' Laboratories, was tried in fifteen cases.

The drug was injected intramuscularly, 1 c.c. on each of two consecutive days in fourteen cases (1171-1184) and 1 c.c. on each of three consecutive days in one case (1185). All the cases were adult males, infected either in Macedonia, East Africa or Egypt. In each instance a diagnosis of simple tertian malaria was made microscopically, and in all cases parasites were present in the blood on the day treatment commenced. Blood examinations were made daily.

The results are given in the Table, which also contains the following additional information:—Place of infection and interval in



months between present treatment and (*a*) first admission to a hospital for malaria, (*b*) leaving infected area, (*c*) arrival in England.

In the Table:—

T. = simple tertian trophozoites or schizonts.

G. = simple tertian gametes.

Neg. = no parasites found.

\* = intramuscular injection of 1 c.c. of collosol manganese.

### CONCLUSION

Collosol manganese in the doses used is of no value in the treatment of simple tertian malaria.





# THE SPREAD AND INCIDENCE OF INTESTINAL PROTOZOAL INFECTIONS IN THE POPULATION OF GREAT BRITAIN

## I. CIVILIANS IN LIVERPOOL ROYAL INFIRMARY II. ARMY RECRUITS

BY

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AND

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*(Received for publication 22 Nov., 1918)*

### INTRODUCTION

In a preliminary note (1917) we and our colleagues recorded the results of the protozoological examination of the stools of a small number of persons who had never been out of this country. The results obtained were of sufficient interest and importance to show the need for further work, and during the past year the investigation has been extended to the examination of various sections of the population. Our findings have been presented briefly by Professor Yorke (1918), but we think it worth while, in a series of short communications, to give further details of the work, and to furnish what information we have been able to obtain regarding some of the more interesting cases.

#### I. CIVILIANS IN LIVERPOOL ROYAL INFIRMARY

The cases examined were mainly surgical. A comparatively small number had been admitted for intestinal complaints, but no selection of the cases was made, and men, women and children were included in our examinations at random. It was possible to make only one examination of the stools, and in reviewing our results it is

important to bear this fact in mind. The results are given in the following table :—

TABLE I.

Showing percentage of cases infected with intestinal protozoa.\*

	Number examined	<i>E. hist.</i>	<i>E. coli</i>	<i>E. nana</i>	<i>G. int.</i>	<i>C. mesnili</i>
Males ...	309	1·9	5·5	3·5	7·1	1·0
Females ...	141	0·7	9·2	—	3·5	2·8
Total ...	450	1·5	6·7	2·4	6·0	1·5

*Trichuris trichiura* eggs 1 case, *Oxyuris vermicularis* eggs 1 case, Iodine cysts 1 case.

We are not quite certain what number of cases is required to constitute a fair sample of any population, but an analysis of the results obtained at the first examination of one thousand five hundred dysentery cases examined in this laboratory indicates that at least five hundred should be examined before the findings based on a single examination may be taken as giving a reliable idea of the incidence of protozoal infections. As the two groups into which we have divided the Infirmary population are much smaller than this, the differences in the results cannot be regarded as having any significance. The main point of interest is that protozoal infections are not uncommon in the general population in Liverpool.

The following brief histories of the seven carriers of *E. histolytica* have been obtained :—

J. McK.	Age 24.	Male.	Native of Liverpool. Employed in Chemical works, St. Helens. Father a seaman.
J.J.	Age 14.	Male.	Native of Liverpool. Still at school.
J.S.	Age 54.	Male.	Native of Liverpool. Dock labourer.
D.B.	Age 10.	Male.	Never been out of Liverpool. Schoolboy. Father been in Navy for considerable number of years, recently discharged.
W.G.	Age 18.	Male.	Boiler-maker's labourer, Liverpool. Father a seaman, recently retired.
J.P.	Age 12.	Male.	Never been out of Liverpool. Schoolboy. Father a soldier who has been home once from France.
M.T.	Age 46.	Female.	Native of Liverpool. No member of family ever abroad.

\* The protozoa here dealt with are *Entamoeba histolytica* (Schaudinn), *E. coli* (Lösch), *E. nana* (Wenyon and O'Connor), *Giardia (Lambli) intestinalis* (Lambl) and *Cobilomastix (Tetramitus) mesnili* (Wenyon).

While it is quite impossible to determine the source of the infection with *E. histolytica* in these seven cases, the particulars obtained convey a suggestion that in some of the infected cases the organism may originally have been introduced by relatives. The origin of *E. histolytica* infections in this country will, however, be considered later.

## II. ARMY RECRUITS

Through the kindness of Capt. Glynn, R.A.M.C., facilities were obtained whereby we were enabled to make examinations of the stools of young army recruits stationed in a camp near Liverpool. This work was commenced in April, 1917. The number of recruits examined totalled one thousand and ninety-eight, each case receiving one examination. The men were examined in batches at different times of the year. The results are shown in Table II, which also gives the average length of time the recruits had been in camp before examination.

TABLE II.  
Showing percentage of cases infected with intestinal protozoa.

	Number examined	Average length of sojourn in camp	Date of examination	<i>E. hist.</i>	<i>E. coli</i>	<i>E. nana</i>	<i>G. int.</i>	<i>G. mesnili</i>
Batch I	263	2-3 months	1917 April-May	3.0	12.1	?	4.5	—
„ II	241	2-3 months	August	6.6	23.2	6.6	7.5	1 case
„ III	230*	5 months	October 1918	3.9	14.8	5.7	6.1	—
„ IV	98	1 month	April	6.1	21.4	6.1	8.2	—
„ V	84	2.5 days	May	8.2	22.4	6.0	11.8	1 case
„ VI	104	9 days	May	5.8	17.4	12.5	6.7	—
„ VII	78	16 days	June	12.8	23.1	9.0	10.2	—
Total	1098	—	—	5.6	18.2	5.5	7.0	2 cases

*Trichuris trichiura* eggs 3 cases, Iodine cysts 5 cases.

\* The great majority of these had been in the camp hospital for various lengths of time.

We have already stated that five hundred is probably the minimum number of cases that should be examined in order to obtain a reliable idea of the incidence of protozoal infections. We can attach no significance, therefore, to the varying percentages of infected cases among the different batches examined, as shown in the above table. The figures for the total number of cases examined are remarkably high, and it was not anticipated that protozoal infections would be found to be so prevalent among soldiers who had never been out of this country. It is not clear why a greater prevalence of infections should occur among the recruits than among the ordinary population of Liverpool as seen in the Royal Infirmary sample (see Table I). We have to consider, therefore, whether the concentration of men in camps in this country has not been a factor which may have helped in the dissemination of intestinal protozoa. There is no evidence from the figures given in Table II of any increase in the number of infected cases as the length of residence in camp increased. The results obtained from the examination of men who had been in camp a short time (see Batches V, VI and VII) indicate that they were as rich in protozoal infections as those who had remained for longer periods. It seems, therefore, that the infections were present while the men formed part of the normal civilian population of the country, and it does not appear possible to give a satisfactory explanation of the difference between the two groups, viz. : Recruits and the Infirmary population. A suggestion which we put forward in the most tentative manner is conveyed by certain facts we ascertained regarding the ages of the individuals we examined in the Infirmary. There is an indication, as shown by Table III, that infections were more prevalent among the younger members of the population. Unfortunately the question of age did not present itself to us until the investigation was well advanced, and we were able to obtain this particular for only two hundred and two men of the Royal Infirmary series. These have been divided into two groups (Table III) according to whether they were over or under 19 years of age. We chose this age because almost all the Army Recruits were under 19 years. The numbers are too small to give more than a suggestion of the facts, but it is possible that, if the Infirmary cases

had been selected so as to be of the same age as the recruits, the incidence of protozoal infections in the former would have been nearly the same as in the latter. If age is a determining factor in the way suggested, it follows that protozoal infections disappear from the intestine in the course of time. At present we have no data on this question, and direct evidence could be obtained only by prolonged examinations of known infected cases. We shall return to the matter in a later paper in discussing the work done among children.

The general conclusion reached from the present work is that intestinal protozoal infections are by no means uncommon in the population of these islands. In the absence of further facts, it will serve no useful purpose to discuss in detail the probable origin of these infections. The protozoa concerned may have occurred

TABLE III.

Showing the number of cases infected among 202 men grouped according to age.

OVER 19 YEARS OF AGE					UNDER 19 YEARS OF AGE				
Number examined...					Number examined				
	...	...	...	164		...	...	...	38
<i>E. histolytica</i>	...	...	...	2 cases	<i>E. histolytica</i>	...	...	...	4 cases
<i>E. coli</i>	...	...	...	10 "	<i>E. coli</i>	...	...	...	5 "
<i>G. int.</i>	...	...	...	8 "	<i>G. int.</i>	...	...	...	10 "

among persons in this country for a very long time, i.e. they may be regarded as indigenous, or they may have been recently introduced by the large number of returned soldiers, many of whom were carriers of *E. histolytica* and other protozoa. But apart from the return of infected soldiers during this and previous wars, another source of infection exists in the constant arrival of seafaring people, many of them no doubt from tropical and sub-tropical regions. This source of infection has existed for centuries, and would be sufficient in the course of time (presuming the primary origin of the infections to be tropical) to result in a general distribution of the organisms throughout the population. In this connection, we may mention that of four hundred and fifty non-dysenteric naval and military patients examined by us in a previous investigation, eighty-two

were sailors, of whom five were found to be carriers of *E. histolytica*, ten were infected with *E. coli*, ten with *G. intestinalis*, and one with *C. mesnili*. It is now practically impossible to obtain any reliable idea of the incidence of protozoal infections in the population of this country before the war, and in consequence we cannot estimate the effect of the return of large numbers of carriers.

Some of the results we have obtained seem to indicate that there may be occupational differences in the incidence of infection. The seventy-eight men comprising Batch 7 (Table II) were miners, and it will be seen that the percentage of infected cases among them was high. Although the number is small, the results suggest a further line of enquiry.

Particulars of the sixty-two recruits infected with *E. histolytica* are given in Table IV. The particulars give some idea of the distribution of the parasite, and they show also that it is found among persons of various occupations.

TABLE IV.

Particulars relating to carriers of *Entamoeba histolytica* among Army Recruits who have never been out of Great Britain.

No. of Case	Age, in years	Place of Residence	Civil Occupation	Date of joining Army and going to training camp	Date of examination
1	18	Manchester ... ..	Clerk ... ..	Mar. 12, 1917	April 19, 1917
2	18	Ashton-under-Lyne	Spinner ... ..	Mar. 7, 1917	April 19, 1917
3	18	Chorley ... ..	Bleaching Works Employee	Mar. 14, 1917	April 19, 1917
4	18	Manchester ... ..	Carter ... ..	Mar. 7, 1917	May 10, 1917
5	18	Liverpool ... ..	Dock Labourer	Mar. 12, 1917	May 10, 1917
6	19	Wigan ... ..	Carter ... ..	Mar. 5, 1917	May 10, 1917
7	18	Burnley ... ..	Shop Assistant	Mar. 12, 1917	May 10, 1917
8	18	Manchester ... ..	Packer ... ..	Mar. 12, 1917	May 10, 1917
9	18	Manchester ... ..	Warehouseman...	July 18, 1917	Aug. 8, 1917
10	—	—	—	—	Aug. 8, 1917

TABLE IV—*continued.*

No. of Case	Age, in years	Place of Residence	Civil Occupation	Date of joining Army and going to training camp	Date of examination
11	18	Aberdare ... ..	Clerk ... ..	July 10, 1917	Aug. 8, 1917
12	19	Carmarthen ... ..	Spinner ... ..	July, 1917	Aug. 8, 1917
13	18	Ellesmere ... ..	Butcher ... ..	July, 1917	Aug. 8, 1917
14	18	Birkenhead ... ..	Clerk ... ..	July 19, 1917	Aug. 8, 1917
15	18	Salop ... ..	Farm Labourer	June 11, 1917	Aug. 28, 1917
16	18	Leeds... ..	Farm Labourer	June 12, 1917	Aug. 28, 1917
17	19	Abergavenny ... ..	Engine Cleaner	June 7, 1917	Aug. 28, 1917
18	18	Stratford ... ..	Motor Mechanic	May, 1917	Aug. 28, 1917
19	18	Blackpool ... ..	Chemist ... ..	April 4, 1917	Aug. 28, 1917
20	18	Nr. Oswestry ... ..	Miller ... ..	May 16, 1917	Aug. 28, 1917
21	18	Swansea ... ..	Steel Worker ... ..	April, 1917	Aug. 28, 1917
22	18	South Wales ... ..	Collier ... ..	July 1, 1917	Aug. 28, 1917
23	18	Abersychan ... ..	Carter ... ..	July 1, 1917	Aug. 28, 1917
24	18	Bootle ... ..	Blacksmith ... ..	April, 1917	Aug. 28, 1917
25	18	Liverpool ... ..	Grocer ... ..	Aug. 2, 1917	Oct. 5, 1917
26	18	Nr. Preston ... ..	Greengrocer and Cabdriver	July 10, 1917	Oct. 4, 1917
27	18	Aberystwyth... ..	Engine Cleaner	July 11, 1917	Oct. 6, 1917
28	18	Rhondda, South Wales	Miner ... ..	Aug. 14, 1917	Oct. 17, 1917
29	18	Liverpool ... ..	Shipyards Labourer	July 10, 1917	Oct. 16, 1917
30	18	Rhondda Valley ... ..	Miner ... ..	Jan. 1917	Oct. 18, 1917
31	18	Llanelly ... ..	Fitter's Mate ... ..	Sept. 5, 1917	Oct. 31, 1917
32	18	Dowlais, South Wales	Electrician ... ..	June 13, 1917	Oct. 30, 1917
33	18	St. Albans ... ..	Vanman and Grocer's Assistant	Sept. 17, 1917	Oct. 10, 1917
34	18	Bethesda ... ..	Slate Quarryman	Mar. 3, 1918	April 10, 1918
35	18	St. Helens ... ..	Glass Works Labourer	Feb. 15, 1918	April 10, 1918
36	18	Kirkby Lonsdale ... ..	Joiner ... ..	Mar. 24, 1918	April 10, 1918
37	18	Treherbert, South Wales	Collier ... ..	Mar. 13, 1918	April 10, 1918

TABLE IV—*continued.*

No. of Case	Age, in years	Place of Residence	Civil Occupation	Date of joining Army and going to training camp	Date of examination
38	18	Cardiff ... ..	Collier ... ..	Feb. 2, 1918	April 10, 1918
39	18	Oldham ... ..	Railway Clerk ...	Mar. 3, 1918	April 10, 1918
40	18	Carlisle ... ..	Cotton Spinner	May 4, 1918	May 7, 1918
41	18	Earlestown ... ..	Glass Worker ...	May 2, 1918	May 7, 1918
42	18	Wigan ... ..	Collier ... ..	May 6, 1918	May 7, 1918
43	17	Tonyrefail, South Wales	Collier ... ..	May 3, 1918	May 7, 1918
44	18	Bolton ... ..	Textile Fitter ...	May 4, 1918	May 7, 1918
45	18	Liverpool ... ..	Carter ... ..	May 6, 1918	May 7, 1918
46	18	Liverpool ... ..	Dock Porter ...	May 4, 1918	May 7, 1918
47	18	Liverpool ... ..	Labourer ... ..	May 13, 1918	May 22, 1918
48	18	Blackburn ... ..	Weaver ... ..	May 11, 1918	May 22, 1918
49	18	Carlisle ... ..	Engine Cleaner	May 4, 1918	May 22, 1918
50	18	Liverpool ... ..	Machinist ... ..	May 9, 1918	May 22, 1918
51	18	Cleator Moor ... ..	Clerk ... ..	May 9, 1918	May 22, 1918
52	18	Wigan ... ..	Baker ... ..	May 9, 1918	May 22, 1918
53	19	Caerau, South Wales	Collier ... ..	May 25, 1918	June 11, 1918
54	26	Tonyrefail, ... .. South Wales	Collier ... ..	May 24, 1918	June 11, 1918
55	24	Carmarthen ... ..	Collier ... ..	May 26, 1918	June 11, 1918
56	22	Pontypool, South Wales	Collier ... ..	May 25, 1918	June 11, 1918
57	25	Pontypool, South Wales	Collier ... ..	May 24, 1918	June 11, 1918
58	21	Tonyrefail, South Wales	Collier ... ..	May 26, 1918	June 11, 1918
59	23	Pontypool, South Wales	Collier ... ..	May 23, 1918	June 11, 1918
60	23	Abertysswg ... ..	Collier ... ..	May 23, 1918	June 11, 1918
61	27	Pontllanfraith, South Wales	Collier ... ..	May 26, 1918	June 11, 1918
62	—	Brynamman, South Wales	Collier ... ..	May 29, 1918	June 11, 1918



We give, finally, in Table V a comparison of our results with those obtained by ourselves and others from the examination of soldiers who have been abroad.

TABLE V.

Showing percentage of cases infected with intestinal protozoa.

	Recruits never out of Great Britain (Table II above)	Healthy troops in Alexandria (Wenyon and O'Connor)	Dysenteric convalescents (Mackinnon)	Non-dysenteric convalescents (Mackinnon)	Dysenteric convalescents (Liverpool)	Non-dysenteric convalescents (Liverpool)
Number examined	1098	1979	914	766	1713	450
<i>E. hist.</i> ...	5.6	5.3	4.9	3.5	5.9	6.4
<i>E. coli</i> ...	18.2	20.0	...	...	15.5	14.2
<i>E. nana</i> ...	5.5	0.5	...	...	...	...
<i>G. int.</i> ...	7.0	4.8	...	...	11.3	10.8
<i>C. mesnili</i>	2 cases	1.1	...	...	...	...

All the findings recorded in Table V are based on a single examination per case, and the remarkable fact appears that protozoal infections are as prevalent among soldiers who have never been out of this country as among troops in Egypt and those who have been invalided home from various fronts. It therefore becomes impossible to say whether the men examined in Egypt actually became infected before or after they left this country. Wenyon and O'Connor found that 13.5 per cent. of five hundred and twenty-four healthy natives in prison in Alexandria were infected with *E. histolytica*, and concluded 'that the native of Egypt is acting as a reservoir of infection for the intestinal protozoa with which the British troops have become and are becoming infected.' In view of this statement, the results we have obtained are of considerable interest.

There is apparently, however, one marked difference between persons infected with *E. histolytica* at home and abroad. A considerable percentage of those abroad become victims of acute amoebic dysentery, while at home the number of such cases is comparatively

small. We agree with Wenyon and O'Connor in thinking that the danger of amoebic dysentery becoming widespread in England is remote. While they base their conclusion largely on the belief that the conditions necessary for the spread of cysts of *E. histolytica* do not exist in any marked degree, we would remark that the evidence produced in the present investigation points to the common occurrence of the organism in persons in this country. If amoebic dysentery does not occur commonly it is not because *E. histolytica* is rare. The reason is probably to be found in a combination of factors which are now becoming recognised and need not be discussed here.\*

In conclusion, we wish to express our gratitude to Professor W. Yorke for the interest he has always taken in the progress of this investigation. We wish to mention, also, that in the earlier part of the investigation some of the examinations were made by our former colleagues Mr. H. F. Carter and Dr. D. L. Mackinnon, to whom we tender our thanks. We are much indebted to the military authorities at Kinmel Camp for giving us facilities for carrying out our work among recruits, and we take this opportunity of expressing our thanks to them. Thanks are also due to Sergeant Fann who, by kind permission of Captain Glynn, rendered invaluable help in the collection of the specimens from recruits.

### SUMMARY

Among four hundred and fifty civilians (men, women and children) in Liverpool Royal Infirmary, seven, or 1·5 per cent., were found by one examination per case to be carriers of *Entamoeba histolytica*.

Among one thousand and ninety-eight healthy young recruits, one examination revealed sixty-two, or 5·6 per cent., to be infected with *E. histolytica*.

Reasons have been given for thinking that the numerical differences between the results for the two\* groups are probably not significant. Whereas the young recruits form a specially selected

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\* See Wenyon and O'Connor (1917), and Dobell's review of their work (1918).

section of the population, the Infirmary cases constitute a very mixed population.

The non-pathogenic intestinal protozoa (*E. coli*, *E. nana*, *Giardia* and *Chilomastix*) are commonly distributed in the population of this country.

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# THE SPREAD AND INCIDENCE OF INTESTINAL PROTOZOAL INFECTIONS IN THE POPULATION OF GREAT BRITAIN

## III. CHILDREN

BY

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(Received for publication 10 December, 1918)

In a previous paper (1919) we directed attention to the fact that intestinal protozoal infections were frequent among the younger persons we examined in Liverpool Royal Infirmary. To obtain further data on this point we decided to examine the stools of children. Material for the investigation was obtained at the Liverpool Infirmary for Children, where all the patients are under 12 years of age. The cases examined were in hospital for various diseases, the great majority being non-intestinal. A small number admitted with summer diarrhoea will be considered later. The protozoal findings, based on a single examination per case, are given in Table I.

TABLE I.

Showing percentage of cases infected with intestinal protozoa.

		Number examined	<i>E. histolytica</i>	<i>E. coli</i>	<i>E. nana</i>	<i>Giardia intestinalis</i>	<i>Cbilomastix mesnili</i>
Boys...	...	321	1.9	10.3	3.4	14.6	0.3
Girls	...	227	1.8	12.3	1.8	13.2	4.1
Total	...	548	1.8	11.1	2.7	14.1	1.8

The following Helminthic infections were found :—

*Trichuris trichiura* ... in 3 cases  
*Oxyuris vermicularis* ... in 3 cases  
*Taenia saginata* ... in 2 cases  
*Hymenolepis nana* ... in 1 case

Iodine cysts were found in one case.

The total number of cases examined is probably large enough to give a fairly reliable idea of the incidence of protozoal infections among children in Liverpool.

*Giardia intestinalis* appears to be the commonest protozoon, although in our records for adults *E. coli* has always been the most prevalent. Arrangement of the cases according to sex gives somewhat small and rather unequal numbers in the two groups, nevertheless the figures in Table I indicate that infections are equally common among boys and girls.

The number of children examined at different ages and the infections discovered in each age group are shown in Table II.

TABLE II.

Age in years	Number of cases examined	<i>E. hist.</i> cases	<i>E. coli</i> cases	<i>E. nana</i> cases	<i>G. int.</i> cases	<i>C. mesnili</i> cases
0-1	50	...	...	...	...	...
1-2	79	...	4	...	6	1
2-3	74	1	9	2	18	1
3-4	56	2	12	1	9	2
4-5	66	...	10	2	12	2
5-6	43	1	5	1	5	...
6-7	44	2	6	2	10	1
7-8	36	1	5	3	4	1
8-9	42	...	4	2	5	1
9-10	27	...	2	...	4	...
10-11	23	2	4	2	3	1
11-12	8	1	...	...	1	...

Among fifty children, under one year of age, no infections were found. Children in their second year, however, were discovered to be infected. *Giardia* and *Chilomastix* were detected in a girl of one year and two months, while a boy of one year and four months was infected with *E. coli* and *Giardia*. *E. histolytica* and *E. nana* were discovered in a girl just three years of age. It appears then

that children may become infected with intestinal protozoa soon after they are twelve months old.

The numbers in the age groups shown in Table II are too small to allow of generalisations from the results. We have therefore arranged in two groups all the cases that were over one year of age (Table III). Since there is no evidence that children under one year are infected, the fifty cases coming within this category have been excluded.

TABLE III.

Children 1-5 years of age.					Children 5-12 years of age				
Number examined ...	...	...	...	275	Number examined ...	...	...	...	223
<i>E. histolytica</i> ...	...	...	...	1.1	<i>E. histolytica</i> ...	...	...	...	3.1
<i>E. coli</i> ...	...	...	...	12.7	<i>E. coli</i> ...	...	...	...	11.6
<i>E. nana</i> ...	...	...	...	1.8	<i>E. nana</i> ...	...	...	...	4.5
<i>G. intestinalis</i> ...	...	...	...	16.4	<i>G. intestinalis</i> ...	...	...	...	14.3
<i>C. mesnili</i> ...	...	...	...	2.2	<i>C. mesnili</i> ...	...	...	...	1.8

It will be seen from Table III that the common protozoa *E. coli* and *G. intestinalis* are equally prevalent in the two groups. The number of cases infected with *E. histolytica*, *E. nana* and *C. mesnili* respectively is, however, too small to justify any close comparison. The chief interest of the results lies in the fact that all the common intestinal protozoa of man are to be found in children not exceeding five years of age.

It is of interest, therefore, to compare the general results for children with those obtained for other sections of the population examined. Comparative figures are given in Table IV.

The children in the Liverpool Infirmary for Children and the adults in the Royal Infirmary constitute, so far as we know, very similar samples of the general population, the only outstanding difference between the two groups being age. It seems admissible, therefore, to make a fairly close comparison of the results obtained for the two series. Among children the commonest protozoon is

*G. intestinalis* and if we exclude the fifty cases who were under one year of age, the percentage of infection with this flagellate becomes 15.5.\* On the other hand, only 6 per cent. of the adult population as seen in the Royal Infirmary sample were infected with *G. intestinalis*. Table IV also shows that among army recruits of 18 years of age, the flagellate was found in only 7 per cent. We think there must be some reason for the decidedly greater prevalence of *G. intestinalis* among children compared with adults. In our previous paper we

TABLE IV.

Showing percentage of cases infected with intestinal protozoa among Children, Adults and Army Recruits never out of Britain.

	Children	Adults	Army Recruits
No. examined ... ..	548	450	1098
<i>E. histolytica</i> ... ..	1.8	1.5	5.6
<i>E. coli</i> ... ..	11.1	6.7	18.2
<i>E. nana</i> ... ..	2.7	2.4	5.5
<i>G. intestinalis</i> ... ..	14.1	6.0	7.0
<i>C. mesnili</i> ... ..	1.8	1.5	2 cases

made the suggestion that intestinal protozoa may disappear from the intestine in the course of time, and it seems that *G. intestinalis* may be a case in point. It may be that the flagellate is mainly a parasite of children and becomes rarer in older people.

In the case of adults the chances of becoming infected are probably greatly reduced on account of their usually greater cleanliness. The chance of adults becoming infected must, however, by no means be entirely excluded. Nevertheless, instead of the percentage of *G. intestinalis* infection in adults being greater or even the same as in children it is very much less, and we can offer no explanation of this remarkable fact other than that already advanced.

\* In discussing the incidence of infection among children we think it important to remember that liability to infection does not appear to occur until the child has entered his second year (see Table II). If any series of children happened to contain a large number under one year of age it is clear that the results would be correspondingly low.



The number of cases infected with the flagellate—*C. mesnili*—is too small to warrant any discussion of the results. This is true also of the amoebic infections with the exception of *E. coli*. This amoeba is not so prevalent among children as among recruits, although it appears commoner in the children than in the adult section of the population. It is possible that *E. coli* infections are also lost in the course of time. The figures in Table IV support this suggestion.

It is necessary to point out in connection with the foregoing remarks on the probable loss of infections that the evidence at our disposal is indirect. Before the question can be finally determined it will be necessary to examine given infected cases for prolonged periods, and it seems that this would now form a promising line of enquiry regarding the behaviour of the intestinal protozoa of man. We would also mention that the parasites in all probability do not behave alike. On this point, however, we have no evidence.

Before proceeding to give histories of some of the cases infected with *E. histolytica* we may mention that thirty-two of the children examined were admitted to hospital suffering from summer diarrhoea. Of these, seventeen were under one year of age and were negative. Among the remaining fifteen, three infections with *E. coli* were found. There is no evidence, therefore, from this small number of cases, that intestinal protozoa are in any way connected with the occurrence of summer diarrhoea in children.

In order to obtain a closer insight into the actual process of spread of these protozoal infections we have singled out certain cases, chiefly those infected with *E. histolytica*, and have examined the whole family of which each one was a member. In only one family were we able to examine the parents as well as the children and the records in this case (Family I) proved of great interest. In all the other families we examined the children only. Table V gives the results.

It is of great importance to keep clearly in mind that these are the results of one examination only.\* They are therefore minimum results. At least the infections recorded were present, probably, in fact almost certainly, others also.

\* The child, however, who was the starting point of the investigation in each family, was examined twice.

TABLE V.

Family	Case	Age	Protozoa present					Non-protozoal Infections	
			<i>E. b.</i>	<i>E. c.</i>	<i>E. n.</i>	<i>G. i.</i>	<i>Cb. m.</i>	I. cysts	Hymen- olepis eggs
I.	J. S.	41	+	...	+	...	...	...	...
	L. S.	41	+	+	+	...	...	...	...
	L. S.	16	+	+	+	...	...	...	...
	F. S.	13	+	+	+	...	...	...	...
	Ja. S.	11	+	+	+	...	...	...	...
	J. S.	9	...	+	...	...	+	...	+
	M. S.	7	+	+	+	+	...	...	...
	D. S.*	3	+	...	+	+	...	...	...
II.	E. P.	13	+	+	+	+	...	...	...
	S. P.*	11	+	+	...	...	+	...	...
	E. P.	9	+	+	+	...	...	...	...
	J. P.	5	+	...	+	+	...	...	+
III.	M. C.*	7	+	+	...	...	+	+	...
	C.	5	+	+	...	...	+	+	...
	C.	3	...	+	...	+	...	...	...
	C.	5/12	...	...	...	...	...	...	...
IV.†	W. H.	10	...	+	...	...	...	...	...
	E. H.*	6	+	...	...	...	...	...	...
	W. C.	7	...	...	...	...	...	...	...
V.	J. W.*	7	+	+	+	...	...	...	...
	H. W.	4	+	...	+	...	...	...	...
	F. W.	1½	...	+	...	+	...	...	...
VI.†	H. M.*	11	+	+	...	...	...	...	...
	A. J.	5	...	+	+	...	...	...	+
	L. J.	3	...	...	...	...	...	...	...
VII.	G. T.	6	...	+	+	...	+	...	...
	E. T.*	3½	...	+	+	+	+	...	...

\* The original case in the Children's Infirmary.

† Two related families occupied the same house.

It is clear from Table V that within certain families infections are much more common than in the general population of children. This is strikingly seen in Family I, where, in one family only, there are almost as many *E. histolytica* infections as we have found in the 548 cases taken from single members of different families. This applies also to the other infections particularly to *E. coli* and *E. nana*.

There are at least two possible ways in which this state of affairs may have been brought about. (1) A single member (or some small number of members) of the family has become infected in a way at present unknown and from this source the infection has spread to the other members of the family. Intercourse between members of the same family is close and long-continued and therefore many more chances of infection must occur within the limits of the family than beyond them. It is therefore not surprising that, once there is a source of infection within the family, the infection should spread throughout the family. (2) The whole family or those members of it who have similar infections may have been infected simultaneously, for instance by all eating food from the same contaminated source. In this case there would be no subsequent spread within the family. We think the former method the more probable, for if whole families or considerable proportions of them can be simultaneously infected from an outside source, it would be expected that the general population of children would show a considerably higher proportion of infections than is actually the case. Bacterial infections such as those spread by contaminated food or water spread rapidly through the population and may even result in epidemics. In the case of intestinal protozoal infections it seems that such families as have here been investigated form, as it were, isolated pockets among a general population fairly free from infection. This is particularly true of *E. histolytica*, the only one of these infections known to be pathogenic.

With regard to the possibility of the fly being a carrier of protozoal infections we can only say that, though most of the families belonged to the poorest section of the population, all the houses we investigated were provided with water-closets and therefore, as a general rule, faeces were not exposed. On the assumption that the infections spread somewhat slowly within the family the fly probably does not play a prominent part as a carrier. Infection however must

occasionally be carried across the limits of a family and the fly may be the agent in this. Exposed faeces do, no doubt, occasionally occur in and about such homes and flies may become the agents which spread the infections among the general population.

With regard to the possible source of these protozoal infections it may be recorded that in each of the families investigated, one member—in six of the families the father, in the seventh a brother—had been abroad and had visited the home after going abroad. In five cases this member of the family was a soldier and in two cases a sailor. It is therefore possible that all the infections had their origin abroad. It is not at all necessary to make this supposition however, for protozoal infections, as we have shown (Matthews and Smith (1919)) are sufficiently common in all sections of the population to warrant the belief that they may have existed in this country before the war.

On the supposition that races producing cysts of definite average size exist in *E. histolytica* and *E. coli* (see Wenyon and O'Connor (1917), Dobell and Jepps (1918), Smith (1918), Matthews (1919)), we thought it worth while to make measurements of the size of the cysts in those infections in which the cysts were present in sufficient numbers. We thought that if the members of the family were all infected from one source they would probably pass cysts of the same average size. The results are given in Table VI.

TABLE VI.

Family	Case	Age	Protozoon	Average diameter of 50 cysts measured ( $\mu$ )
II.	E. P.	13	<i>E. histolytica</i>	12.9
	J. P.	5	<i>E. histolytica</i>	12.8
I.	J. S.	9	<i>E. coli</i>	16.5
	Ja. S.	11	<i>E. coli</i>	16.4
	L. S.	16	<i>E. coli</i>	16.8
	M. S.	7	<i>E. coli</i>	18.3

The evidence does not go far, but such as it is, it points to one race, and therefore presumably one source of infection, for the *E. histolytica* infection in the two members examined of Family II, and to two sources of infection in the four members of Family I.

We wish to express our thanks to Major P. Davidson, R.A.M.C., by whose kind permission we were enabled to obtain specimens from the Children's Infirmary. We also wish to thank the various members of the staff of the Infirmary for their help in the supply of material.

### SUMMARY

1. Stools were examined for intestinal protozoa from 548 children under 12 years of age. *E. histolytica* was found in 1.8 per cent. and the commonest protozoon was *G. intestinalis*, found in 14 per cent.

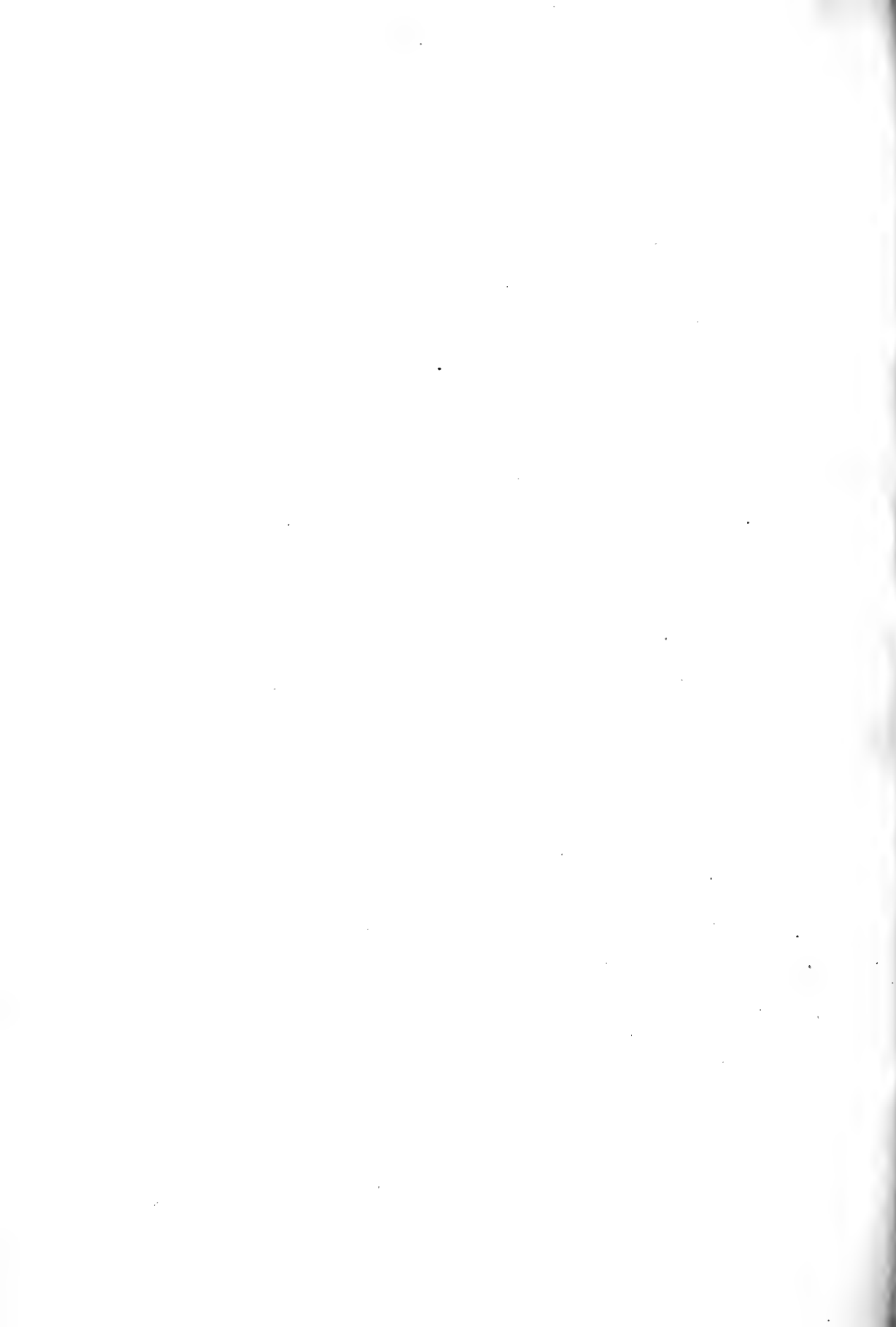
2. Children become infected soon after they are one year old and from this age onward all the common intestinal protozoa are found, irrespective of age or sex.

3. The results have been compared with those from a similar population of adults and it has been observed that *G. intestinalis* in particular is much more common among children.

4. Investigation of whole families of which one member was known to be infected showed that in certain families infections were much more common than in the general population.

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# STUDIES IN THE TREATMENT OF MALARIA

## XXI. ARSENIC IN SIMPLE TERTIAN MALARIA

BY

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Many statements concerning the value of arsenic in the treatment of malaria are found in the literature, but with the exception of a few more recent records relating to organic preparations we have been unable to discover the evidence on which such statements are based.

We proceeded therefore to determine (1) whether inorganic arsenic alone has any action—palliative or curative—in simple tertian malaria, and if so in what dose it should be administered; and (2) whether a combination of arsenic and quinine is more effective than quinine alone. The observations made by us can be divided into the following four groups:—

### GROUP I. Small doses of arsenic.

- A. Liquor arsenicalis\* minims 15 daily, for 8 weeks.
- B. The same as Treatment A, with an injection of Quinine 2 HCl grains 15 intramuscularly on each of the first two days only.

\* The British Pharmacopoeia preparation containing 1 per cent. of arsenious anhydride.

GROUP II. Small doses of arsenic, or of arsenic and strychnine, with quinine.

- C. Liquor arsenici HCl\* minims 15 + Quinine HCl grains 5, daily for 8 weeks.
- D. Liquor arsenici HCl minims 15 and Liquor strychninae HCl minims 15 + Quinine HCl grains 5, daily for 8 weeks
- E. Control Series. Quinine HCl grains 5 daily for 8 weeks.

GROUP III. Large doses of arsenic.

- F. Liquor arsenicalis minims 30 daily, with one or two periods of intermission, for 8 weeks.
- G. The same as Treatment F, with an injection of Quinine 2 HCl grains 15 intramuscularly on each of the first two days only.
- H. Control series. Quinine 2 HCl grains 15 intramuscularly on each of two consecutive days only.

All the cases were adult males, the great majority of whom were infected either in Macedonia or in East Africa (Tables XIV to XIX). In every instance a diagnosis of simple tertian malaria was made microscopically, and in all cases parasites were present in the blood on the day treatment commenced. Blood examinations were made daily.

The records of the observations are given in the tables and charts.

In the tables:—

- o = absence of fever and parasites.
- 1, 2, etc. = number of parasitic febrile relapses, weekly.
- 1\*, 2\*, etc. = number of non-parasitic febrile attacks, weekly.
- P<sup>1</sup>, P<sup>2</sup>, etc. = number of days on which parasites were present weekly.
- Remarks = post-treatment observations.

In the charts:—

- T. = simple tertian trophozoites or schizonts.
- G. = simple tertian gametes.
- Neg. = no parasites found.

NOTE.—A rise of temperature above 100° F., of which the nature is unknown, is termed a *febrile attack*. A similar rise of temperature accompanied by parasites in the blood at the time, or within three days, is termed a *parasitic febrile relapse* or *true relapse*. The term *paroxysm* is used indifferently to denote any febrile disturbance of 100° F. or more.

As we have pointed out elsewhere, the effect of any treatment may be considered from two points of view: (1) the *palliative* action, i.e., the degree to which symptoms are controlled, and the blood kept free

\* The British Pharmacopoeia preparation containing 1 per cent. of arsenious anhydride.



from parasites during the treatment; and (2) the *curative* action, i.e., whether or no relapses occur during the observation period\* after cessation of treatment. In order that the palliative results obtained in the various series of observations may have a comparative value, it is necessary to express the number of cases having true relapses, of those having febrile attacks, and of those having parasitic relapses, as percentages of the total cases undergoing treatment in any particular week. In Tables II, IV, VI, IX and XI, the following sets of figures, each having a comparative value, are given:—

1. The number of cases which had parasitic febrile relapses each week, expressed as a percentage of all cases treated.
2. The number of parasitic febrile relapses experienced per week by each parasitic febrile relapse case.
3. The number of cases which had febrile paroxysms (parasitic and non-parasitic) each week, expressed as a percentage of all cases treated.
4. The number of febrile paroxysms (parasitic and non-parasitic) experienced per week by each febrile (parasitic and non-parasitic) case.
5. The number of cases which had parasitic relapses (febrile and non-febrile) each week, expressed as a percentage of all cases treated.
6. The number of parasitic relapses (febrile and non-febrile) experienced per week by each parasitic relapse (febrile and non-febrile) case.

#### GROUP I. Small doses of arsenic

A. *Liquor arsenicalis* minims 15 daily.† (Cases 1186 to 1188).

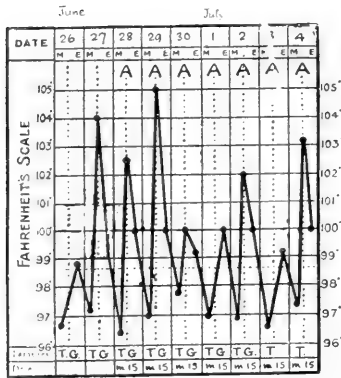
Three cases only were treated in this manner, as it was soon found that *Liquor arsenicalis* in this dose failed to cause the disappearance of parasites from the cutaneous blood or to control the fever. In two cases (1186 and 1187) it was found necessary to alter the treatment after seven days, in the third case (1188) after twenty-two days. Details are given in Charts 1186 to 1188.

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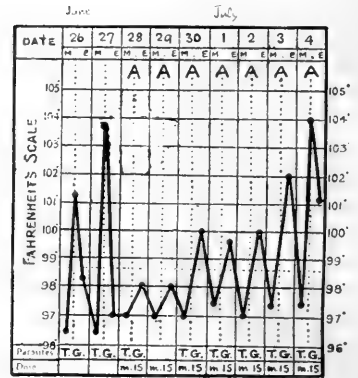
\* This, as in all our previous papers, is 60 days—an entirely arbitrary period.

† *Liq. arsenicalis* ℥ v  
*Aq. chloroformi* ad ℥ i  
 ℥ i. t.d.s.

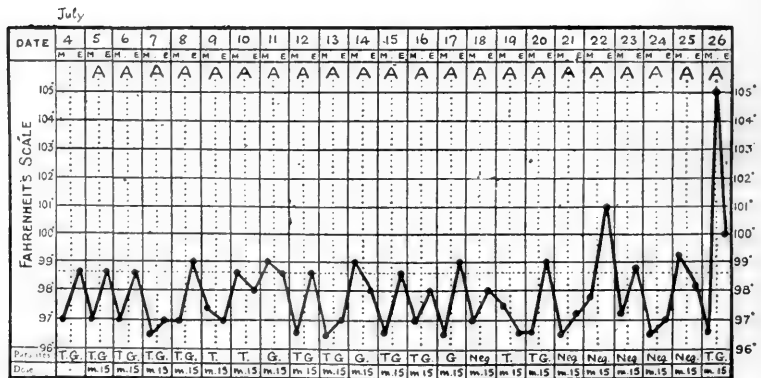
CASE 1186



CASE 1187



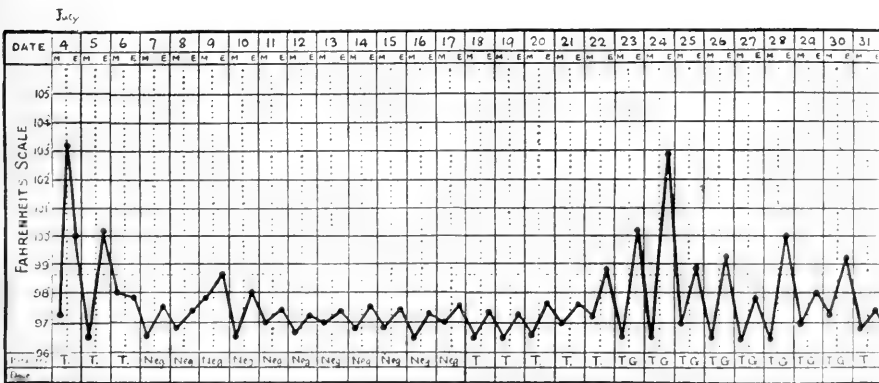
## CASE 1188



B. The same as Treatment A, with an injection of Quinine 2 HCl grains 15 intramuscularly on each of the first two days only (Cases 1189 and 1190).

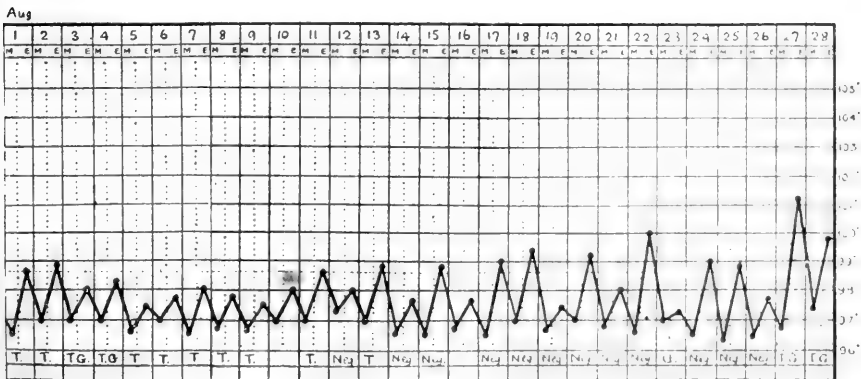
The object of this series of observations was to determine whether, having caused the disappearance of parasites from the cutaneous blood and having controlled symptoms by two initial intramuscular injections of quinine, the daily administration of Liquor arsenicalis (minims 15) would suffice to prevent relapses (parasitic or febrile). The two cases treated in this way relapsed on the thirteenth and eighteenth days respectively after the commencement of treatment, and subsequently parasites were found more or less frequently during the course of treatment; consequently it was considered unnecessary to subject further cases to this form of treatment. Details are given in Charts 1189 and 1190.

## CASE 1189 (Part I)

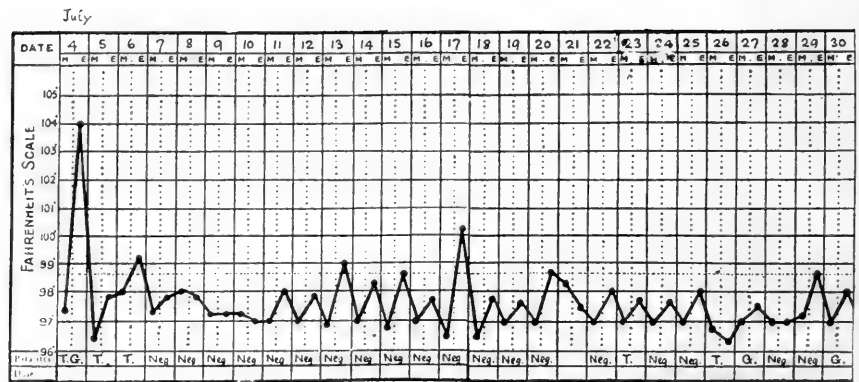


Treatment commenced 5 July.

## CASE 1189 (Part II)

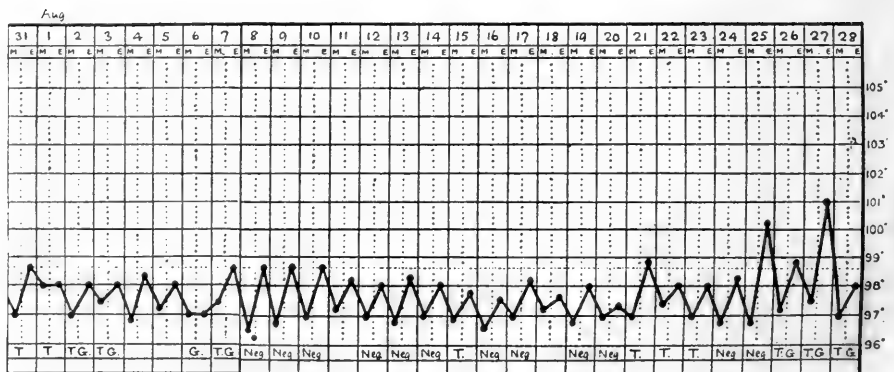


## CASE 1190 (Part I)



Treatment commenced 5 July.

## CASE 1190 (Part II)



## CONCLUSION

Liquor arsenicalis alone, minims 15 daily, fails to cause the disappearance of parasites or to control the symptoms, and does not suffice to prevent relapses (parasitic and febrile) in cases in which parasites and fever have disappeared as the result of two initial intramuscular injections of quinine bihydrochloride.

**GROUP II. Small doses of arsenic, or of arsenic and strychnine, with quinine**

We next proceeded to ascertain whether combinations of (1) arsenic + quinine, or (2) arsenic and strychnine (on account of the alleged tonic effect of the latter) + quinine, were more effective than quinine alone. For this purpose the following three series (C, D, and E) of observations were undertaken.

C. Liquor arsenici HCl minims 15 + Quinine HCl grains 5 daily\* for eight weeks (Cases 1191 to 1218).

In two of the twenty-eight cases treatment was commenced during an apyrexial period; in the remaining twenty-six cases the temperature fell to normal† within five days of the beginning of treatment.

In twenty-one cases parasites disappeared from the cutaneous blood in one to seven days. In the remaining seven (Nos. 1194, 1197, 1206, 1209, 1210, 1214 and 1218) parasites persisted practically throughout treatment (Table XIV).

RELAPSES

*During treatment.* In five of the twenty-eight cases, owing to the severity of the relapses and the grave clinical condition of the patients, it was found impossible to continue the treatment for the full period of eight weeks, e.g., in Cases 1214 and 1215 treatment had to be changed in the eighth week, in Case 1216 in the seventh week, and in Cases 1217 and 1218 in the fifth week. Consequently the number of cases under treatment was in the first week twenty-eight and in the eighth week twenty-three. The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 25·7 per cent of cases treated, (2) non-parasitic febrile attacks 6·3 per cent., (3) febrile paroxysms (parasitic and non-parasitic) 32·0 per cent., (4) parasitic relapses (febrile and non-febrile) 42·4 per cent. (Tables I and II).

*After treatment.* Eighteen of the twenty-three cases observed after cessation of treatment relapsed within the sixty days' observation period. Parasites re-appeared in one to thirty-seven days and

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\* Liq. arsenici HCl ℥ v  
Quininae HCl gr. 1℥  
Aq. chloroformi ad ʒ i  
ʒi. t.d.s.

† By this is meant that the temperature fell to normal and remained so for at least two days.

TABLE I.

C. Summary of results of oral administration of Liquor arsenici HCl minims 15 + Quinine HCl grains 5, daily for 8 weeks, in simple tertian malaria.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated...</b>	<b>28</b>	<b>28</b>	<b>28</b>	<b>28</b>	<b>26</b>	<b>26</b>	<b>25</b>	<b>23</b>
Number of cases having parasitic febrile relapses ...	1	6	5	6	5	7	11	5
Number of cases having non-parasitic febrile attacks ...	1	0	4	5	2	4	1	4
<b>Grand total of all febrile cases...</b>	<b>2</b>	<b>6</b>	<b>9</b>	<b>11</b>	<b>7</b>	<b>11</b>	<b>12</b>	<b>9</b>
Total number of parasitic febrile relapses	1	11	8	14	9	18	23	12
Total number of non-parasitic febrile attacks ...	1	0	4	8	2	4	1	8
<b>Grand total of all febrile paroxysms ...</b>	<b>2</b>	<b>11</b>	<b>12</b>	<b>22</b>	<b>11</b>	<b>22</b>	<b>24</b>	<b>20</b>
Number of parasitic cases (febrile and non-febrile) ...	14	8	9	11	9	11	15	12
Total number of occasions parasites found ...	28	44	47	48	39	43	60	42

TABLE II.

Analysis of TABLE I.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ...	3.6	21.4	17.8	21.4	19.2	26.8	44.0	21.7	<b>25.7</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ...	2.0	1.0	1.8	1.8	1.4	1.6	1.1	1.8	<b>1.5</b>
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated ...	7.1	21.4	32.1	39.2	26.8	42.3	48.0	39.1	<b>32.0</b>
Number of all febrile (parasitic and non-parasitic) paroxysms per febrile case ...	1.0	1.8	1.3	2.0	1.6	2.0	2.0	2.2	<b>1.7</b>
Percentage of all parasitic (febrile and non-febrile) cases per cases treated ...	50.0	28.6	32.1	39.3	34.6	42.3	60.0	52.2	<b>42.4</b>
Number of occasions parasites found per parasitic case ...	2.0	5.5	5.2	4.4	4.3	3.9	4.0	3.5	<b>4.1</b>

febrile relapses occurred in one to thirty-seven days after cessation of treatment. In five of the twenty-eight cases (Nos. 1214 to 1218 the full course of treatment was not completed as the condition was uncontrolled. These therefore should be added to the cases that relapsed, making the total number of failures twenty-three (82 per cent.).

In one of the five cases which did not relapse the post-treatment observation period was less than sixty days, viz., in Case 1195, thirty-seven days. Consequently the minimum number of relapses (those actually observed) was twenty-three and the possible maximum number (those actually observed + the number of cases not relapsing but lost sight of before expiration of the sixty-day post-treatment observation period) was twenty-four, giving a minimum percentage of 82 and a maximum percentage of 86 (Tables XIII and XIV).

D. Liquor arsenici HCl minims 15 and Liquor strychninae HCl minims 15 + Quinine HCl grains 5 daily\* for eight weeks (Cases 1219 to 1243).

In four of the twenty-five cases treatment was commenced during an apyrexial period; in the remaining twenty-one cases the temperature fell to normal within eight days of the beginning of treatment.

In twenty-one cases parasites disappeared from the cutaneous blood in one to seven days. In seven cases (1221, 1222, 1238, 1239, 1241, 1242, and 1243) parasites persisted practically throughout treatment (Table XV).

#### RELAPSES

*During treatment.* In one (1243) of the twenty-five cases, owing to the severity of the relapses and the grave clinical condition of the patient, it was found necessary to alter the treatment in the sixth week. Consequently the number of cases under treatment was in the first week twenty-five and in the eighth week twenty-four. The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 13.2 per cent. of cases

\* Liq. arsenici HCl ℥ 5  
 Liq. strychninae HCl ℥ 5  
 Quininae HCl gr. 1  $\frac{2}{3}$   
 Aq. chloroformi ad  $\frac{5}{8}$  i  
 $\frac{5}{8}$  i. t.i.d.s.

treated, (2) non-parasitic febrile attacks 7·1 per cent., (3) febrile paroxysms (parasitic and non-parasitic) 20·3 per cent., and (4) parasitic relapses (febrile and non-febrile) 37·6 per cent. (Tables III and IV).

*After treatment.* Of the twenty-three cases observed after cessation of treatment seventeen relapsed within the sixty-day observation period. Parasites re-appeared in one to twenty-six days and febrile relapses in seven to twenty-seven days after cessation of treatment. In one (1243) of the twenty-five cases the full course of treatment was not completed as the condition was uncontrolled. This case therefore should be added to the cases that relapsed, making the total number of failures eighteen (75 per cent.).

In two of the six cases which did not relapse the post-treatment observation period was less than sixty days, viz., in Case 1223, forty-two days and in Case 1227, thirty-eight days. Consequently the minimum number of relapses (those actually observed) was eighteen, and the possible maximum number (those actually observed + the number of cases not relapsing but lost sight of before expiration of the full post-treatment observation period of sixty days) was twenty, giving a minimum percentage of 75 and a maximum of 83 (Tables XIII and XV).

E. Control series. Quinine HCl grains 5 daily\* for eight weeks (Cases 1244 to 1269).

In these twenty-six cases the temperature fell to normal within three days of the beginning of treatment.

In eighteen cases parasites disappeared from the cutaneous blood in from one to ten days. In ten cases (Nos. 1244, 1245, 1248, 1249, 1252, 1258, 1261, 1262, 1266 and 1268) parasites persisted practically throughout treatment (Table XVI).

## RELAPSES

*During treatment.* In one (1268) of the twenty-six cases, as the condition was uncontrolled, the treatment was changed in the

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\* Quininae HCl gr.  $1\frac{2}{3}$   
Aq. chloroformi ad  $\frac{5}{8}$  i  
 $\frac{5}{8}$  i. t.d.s.



TABLE III.

**D.** Summary of results of oral administration of Liquor arsenici HCl minims 15 and Liquor strychninae HCl minims 15 + Quinine HCl grains 5, daily for 8 weeks, in simple tertian malaria.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>25</b>	<b>25</b>	<b>25</b>	<b>25</b>	<b>25</b>	<b>24</b>	<b>24</b>	<b>24</b>
Number of cases having parasitic febrile relapses ...	5	3	2	3	6	4	1	2
Number of cases having non-parasitic febrile attacks ...	1	3	2	1	1	2	1	3
<b>Grand total of all febrile cases ...</b>	<b>6</b>	<b>6</b>	<b>4</b>	<b>4</b>	<b>7</b>	<b>6</b>	<b>2</b>	<b>5</b>
Total number of parasitic febrile relapses	10	5	2	6	14	4	1	4
Total number of non-parasitic febrile attacks ...	1	4	2	1	2	3	4	9
<b>Grand total of all febrile paroxysms ...</b>	<b>11</b>	<b>9</b>	<b>4</b>	<b>7</b>	<b>16</b>	<b>7</b>	<b>5</b>	<b>13</b>
Number of parasitic cases (febrile and non-febrile) ...	11	10	9	9	8	8	10	9
Total number of occasions parasites found ...	21	35	31	33	34	26	35	43

TABLE IV.

Analysis of TABLE III.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ...	20.0	12.0	8.0	12.0	24.0	16.7	4.2	8.3	<b>13.2</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ...	2.0	1.7	1.0	2.0	2.3	1.0	1.0	2.0	<b>1.6</b>
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated ...	24.0	24.0	16.0	16.0	28.0	25.0	8.3	20.8	<b>20.3</b>
Number of all febrile (parasitic and non-parasitic) paroxysms per febrile case ...	1.8	1.5	1.0	1.7	2.3	1.2	2.5	2.6	<b>1.8</b>
Percentage of all parasitic (febrile and non-febrile) cases per cases treated ...	44.0	40.0	36.0	36.0	32.0	33.3	41.7	37.5	<b>37.6</b>
Number of occasions parasites found per parasitic case ...	1.9	3.5	3.4	3.7	4.2	3.2	3.5	4.8	<b>3.5</b>

eighth week, and in another case (1269), which developed measles, treatment lasted for six weeks only. Consequently the number of cases under treatment was in the first week twenty-six and in the eighth week twenty-four.

The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 17.0 per cent. of cases treated, (2) non-parasitic febrile attacks 2.0 per cent., (3) febrile paroxysms (parasitic and non-parasitic) 19.0 per cent., and (4) parasitic relapses (febrile and non-febrile) 46.3 per cent. (Tables V and VI).

*After treatment.* Of the twenty-five cases observed after cessation of treatment fifteen relapsed within the sixty-day observation period. Parasites re-appeared in one to thirty-three days and febrile relapses occurred in one to nineteen days after cessation of treatment. In one (1268) of the twenty-six cases the full course of treatment was not completed as the condition was not controlled. This case therefore should be added to the cases that relapsed, making the total failures sixteen (62 per cent.).

In two of the ten cases which did not relapse the post-treatment observation period was less than sixty days, viz., in Case 1246, twenty-three days and in Case 1255, forty days. Consequently the minimum number of relapses (those actually observed) was sixteen, and the possible maximum number (those actually observed + the number of cases not relapsing but lost sight of before expiration of the post-treatment observation period of sixty days) was eighteen, giving a minimum percentage of 62 and a maximum of 69 (Tables XIII and XVI).

## CONCLUSION

Daily administration of arsenic, or of arsenic and strychnine, in small doses (minims 15), in combination with quinine (grains 5) is not more effective than the same dose of quinine alone.

TABLE V.

**E.** Summary of results of oral administration of Quinine HCl grains 5 daily for 8 weeks, in simple tertian malaria.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>26</b>	<b>26</b>	<b>26</b>	<b>26</b>	<b>26</b>	<b>26</b>	<b>25</b>	<b>24</b>
Number of cases having parasitic febrile relapses ...	1	7	6	7	4	2	5	3
Number of cases having non-parasitic febrile attacks ...	0	0	1	0	1	0	0	2
<b>Grand total of all febrile cases ...</b>	<b>1</b>	<b>7</b>	<b>7</b>	<b>7</b>	<b>5</b>	<b>2</b>	<b>5</b>	<b>5</b>
Total number of parasitic febrile relapses	1	12	9	8	4	3	7	4
Total number of non-parasitic febrile attacks ...	0	0	1	0	1	0	0	4
<b>Grand total of all febrile paroxysms ...</b>	<b>1</b>	<b>12</b>	<b>10</b>	<b>8</b>	<b>5</b>	<b>3</b>	<b>7</b>	<b>8</b>
Number of parasitic cases (febrile and non-febrile) ...	11	13	12	11	13	12	13	11
Total number of occasions parasites found ...	27	55	59	47	52	56	53	37

TABLE VI.

Analysis of TABLE V.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ...	3.8	26.9	23.1	26.9	15.4	7.7	20.0	12.5	<b>17.0</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ...	1.0	1.7	1.5	1.1	1.0	1.5	1.4	1.3	<b>1.3</b>
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated ...	3.8	26.9	26.9	26.9	10.2	7.7	20.0	20.8	<b>19.0</b>
Number of all febrile (parasitic and non-parasitic) paroxysms per febrile case ...	1.0	1.7	1.4	1.1	1.0	1.5	1.4	1.6	<b>1.3</b>
Percentage of all parasitic (febrile and non-febrile) cases per cases treated ...	42.3	50.0	46.2	42.3	50.0	40.2	52.0	41.7	<b>46.3</b>
Number of occasions parasites found per parasitic case ...	2.5	4.2	5.0	4.3	4.0	4.7	4.1	3.7	<b>4.0</b>

## GROUP III. Large doses of arsenic

In view of the inefficiency of the small dose of arsenic (minims 15 daily) we proceeded to ascertain whether better results were obtainable by the use of double the dose (minims 30 daily).

F. Liquor arsenicalis minims 30 daily,\* with one or two periods of intermission, for eight weeks (Cases 1270-1283).

It was intended to give the arsenic according to the following plan: four weeks on treatment, one week off treatment, three weeks on treatment; but in only seven of fourteen cases was it found possible to adhere to this plan. In five cases it was found necessary, owing to the development of symptoms of arsenical poisoning, to interrupt treatment on two occasions, and in the remaining two cases owing to loss of sight it was not possible to continue treatment beyond the sixth week (Table VII). In all cases toxic symptoms disappeared shortly after leaving off treatment.

TABLE VII.

Showing mode of administration of arsenic in the various cases in Series F.

Number of cases	Serial numbers	TREATMENT					Duration of treatment
		Weeks on	Weeks off	Weeks on	Weeks off	Weeks on	
7	1270 to 1272 and 1277 to 1280	4	1	3	...	...	8 weeks
5	1273 to 1276 and 1281	3	1	2	1	1	8 weeks
2	1282 and 1283	3	1	2	...	...	6 weeks

In one of the fourteen cases treatment was commenced during an apyrexial period; in the remaining thirteen cases the temperature fell to normal within ten days of the beginning of treatment.

In thirteen of the fourteen cases parasites disappeared from the cutaneous blood in from two to six days. In the remaining case (1278) parasites persisted practically throughout treatment (Table XVII).

\* Liq. arsenicalis ℥ x  
Aq. chloroformi ad ℥ i  
℥i. t.d.s.

## RELAPSES

*During treatment.* In two (1282 and 1283) of the fourteen cases, owing to the development of severe symptoms of arsenical poisoning, it was found impossible to continue the treatment beyond the sixth week. Consequently the number of cases under treatment was in the first week fourteen and in the eighth week twelve. The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 3·8 per cent. of cases treated, (2) non-parasitic febrile attacks 3·5 per cent., (3) febrile paroxysms (parasitic and non-parasitic) 7·3 per cent., and (4) parasitic relapses (febrile and non-febrile) 28·1 per cent. (Tables VIII and IX).

*After treatment.* Eleven of the thirteen cases (85 per cent.), observed after cessation of treatment, relapsed within the sixty-day observation period. Parasites re-appeared in one to thirty-nine days and febrile relapses occurred in one to forty-two days after cessation of treatment (Tables XIII and XVII).

TABLE VIII.

**F.** Summary of results of oral administration of *Liquor arsenicalis minimis* 30 daily, with one or two intermissions, for 8 weeks, in simple tertian malaria.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>14</b>	<b>14</b>	<b>14</b>	<b>14</b>	<b>14</b>	<b>14</b>	<b>12</b>	<b>12</b>
Number of cases having parasitic febrile relapses ...	0	0	1	0	0	2	0	1
Number of cases having non-parasitic febrile attacks ...	1	1	1	1	0	0	0	0
<b>Grand total of all febrile cases ...</b>	<b>1</b>	<b>1</b>	<b>2</b>	<b>1</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>1</b>
Total number of parasitic febrile relapses	0	0	1	0	0	6	0	1
Total number of non-parasitic febrile attacks ...	2	3	1	4	0	0	0	0
<b>Grand total of all febrile paroxysms ...</b>	<b>2</b>	<b>3</b>	<b>2</b>	<b>4</b>	<b>0</b>	<b>6</b>	<b>0</b>	<b>1</b>
Number of parasitic cases (febrile and non-febrile) ...	9	3	2	1	2	4	4	5
Total number of occasions parasites found ...	15	8	3	7	9	14	14	21

TABLE IX.

Analysis of TABLE VIII.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ... ..	0	0	7.1	0	0	14.3	0	8.3	<b>3.8</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ... ..	0	0	1.0	0	0	3.0	0	1.0	<b>0.6</b>
Percentage of all febrile (parasitic and non- parasitic) cases per cases treated ... ..	7.1	7.1	14.3	7.1	0	14.3	0	8.3	<b>7.3</b>
Number of all febrile (parasitic and non- parasitic) paroxysms per febrile case ... ..	2.0	3.0	1.0	4.0	0	3.0	0	1.0	<b>1.75</b>
Percentage of all parasitic (febrile and non- febrile) cases per cases treated ... ..	64.3	21.4	14.3	7.1	14.3	28.6	33.3	41.7	<b>28.1</b>
Number of occasions parasites found per parasitic case ... ..	1.7	2.7	1.5	7.0	4.5	3.5	3.5	4.2	<b>3.6</b>

G. The same as Treatment F with an injection of Quinine 2 HCl grains 15 intramuscularly on each of the first two days only (Cases 1284-1316).

The object of this series of observations was to determine whether, having caused the disappearance of parasites from the cutaneous blood and having controlled symptoms by two initial intramuscular injections of quinine, the daily administration of Liquor arsenicalis minims 30 would suffice to prevent relapses (parasitic and febrile). The arsenic was given according to the following plan: two weeks on treatment, one week off, two weeks on, one week off, two weeks on; all cases were able to tolerate this.

In five of the thirty-three cases treatment was commenced during an apyrexial period; in the remaining twenty-eight cases the temperature fell to normal within two days of the beginning of treatment.

In all cases parasites disappeared from the cutaneous blood in from one to four days (Table XVIII).

TABLE X.

G. Summary of results of administration of Liquor arsenicalis minims 30 daily, with two periods of intermission, for 8 weeks, + Quinine 2 HCl grains 15 intramuscularly on each of the first two days only, in simple tertian malaria.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th
<b>Number of cases treated ...</b>	<b>33</b>	<b>33</b>	<b>32</b>	<b>32</b>	<b>32</b>	<b>32</b>	<b>32</b>	<b>31</b>
Number of cases having parasitic febrile relapses ...	0	0	0	0	1	1	4	1
Number of cases having non-parasitic febrile attacks ...	0	3	3	2	1	3	0	3
<b>Grand total of all febrile cases ...</b>	<b>0</b>	<b>3</b>	<b>3</b>	<b>2</b>	<b>2</b>	<b>4</b>	<b>4</b>	<b>4</b>
Total number of parasitic febrile relapses	0	0	0	0	4	1	5	3
Total number of non-parasitic febrile attacks ...	0	3	7	3	3	5	0	3
<b>Grand total of all febrile paroxysms ...</b>	<b>0</b>	<b>3</b>	<b>7</b>	<b>3</b>	<b>7</b>	<b>6</b>	<b>5</b>	<b>6</b>
Number of parasitic cases (febrile and non-febrile) ...	0	0	0	1	2	1	4	2
Total number of occasions parasites found ...	0	0	0	2	8	6	13	13

TABLE XI.

Analysis of TABLE X.

Week of Treatment	1st	2nd	3rd	4th	5th	6th	7th	8th	Average per week
Percentage of parasitic febrile relapse cases per cases treated ...	0	0	0	0	3.1	3.1	12.5	3.2	<b>2.7</b>
Number of parasitic febrile relapses per parasitic febrile relapse case ...	0	0	0	0	4.0	1.0	1.0	3.0	<b>1.1</b>
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated ...	0	9.4	9.7	6.2	6.2	12.5	12.5	12.0	<b>8.7</b>
Number of all febrile (parasitic and non-parasitic) paroxysms per febrile case ...	0	1.0	2.3	1.5	3.5	1.5	1.2	1.2	<b>1.6</b>
Percentage of all parasitic (febrile and non-febrile) cases per cases treated ...	0	0	0	3.1	6.2	3.1	12.5	6.4	<b>3.9</b>
Number of occasions parasites found per parasitic case ...	0	0	0	2.0	4.0	6.0	3.2	6.5	<b>2.7</b>

## RELAPSES

*During treatment.* In one (1315) of the thirty-three cases, owing to the severity of the relapses and the grave clinical condition of the patient, it was found impossible to continue the treatment beyond the seventh week; in another case (1316) owing to intercurrent disease, treatment was given for two weeks only. Consequently the number of cases under treatment was in the first week thirty-three and in the eighth week thirty-one. The average weekly number, over a period of eight weeks, of cases which had (1) parasitic febrile relapses was 2.7 per cent. of cases treated, (2) non-parasitic febrile attacks 6.0 per cent., (3) febrile paroxysms (parasitic and non-parasitic) 8.7 per cent., and (4) parasitic relapses (febrile and non-febrile) 3.9 per cent. (Tables X and XI).

*After treatment.* Three of the thirty-one cases observed after cessation of treatment relapsed within the sixty-day observation period. Parasites re-appeared in one to fifteen days and febrile relapses occurred in one to nineteen days after cessation of treatment. In one (1315) of the thirty-three cases the full course of treatment was not completed as the condition was uncontrolled. This case therefore should be added to the cases that relapsed, making the total failures four (12.5 per cent.). (Tables XIII and XVIII.)

H. Control series. Quinine 2 HCl grains 15 intramuscularly on each of two consecutive days only (Cases 1317-1346).

In three of the thirty cases treatment was commenced during an apyrexial period; in the remaining twenty-seven cases the temperature fell to normal within three days of the beginning of treatment.

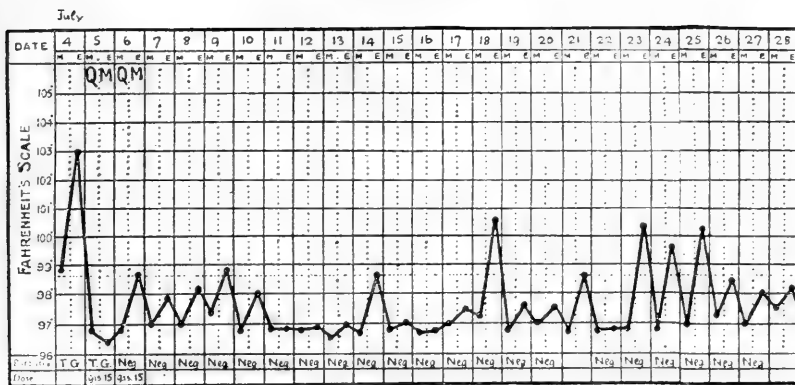
In all cases parasites disappeared from the cutaneous blood in from one to four days (Table XIX).

## RELAPSES

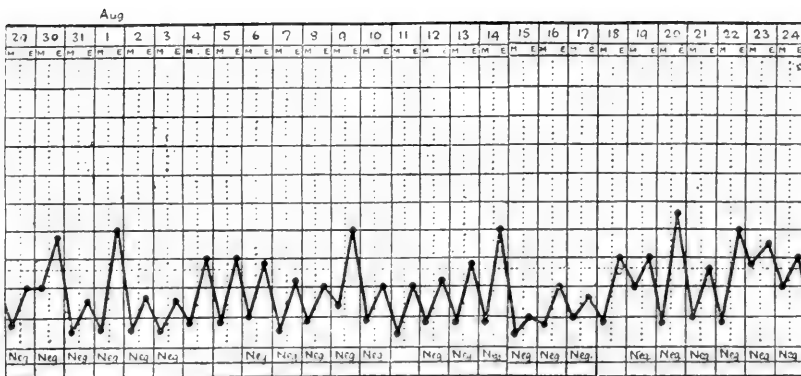
*After treatment.* Twenty-one of the thirty cases (70 per cent.) observed for sixty days after cessation of treatment relapsed. Parasites re-appeared in six to twenty-five days and febrile relapses occurred in nine to twenty-five days after cessation of treatment (Tables XIII and XIX).



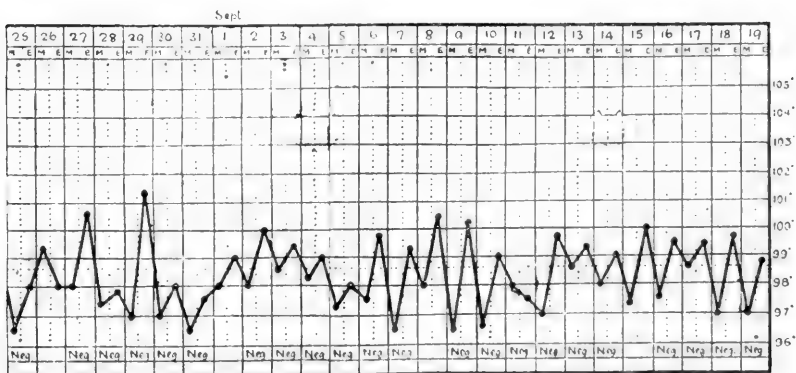
## CASE 132I (Part I)



## CASE 1321 (Part II)



## CASE 1321 (Part III)



## CONCLUSION

As a *palliative*, Liquor arsenicalis minims 30 daily appeared to exert a definite control of the temperature, the average weekly number of cases having parasitic febrile relapses being only 3·8 per cent. of cases treated; on the contrary, however, it failed in many cases to keep the cutaneous blood free from parasites, the average weekly number of cases having parasitic relapses (febrile and non-febrile) being 28·1 per cent. of cases treated. As a *curative*, the treatment was practically valueless, being followed by 85 per cent. of relapses.

The same treatment, however, with two initial injections of Quinine 2 HCl grains 15 gave very different results. The average weekly number of cases having parasitic febrile relapses was 2·7 per cent. of cases treated; but in contradistinction to the previous treatment the average weekly number of cases having parasitic relapses (febrile and non-febrile) was only 3·9 per cent. of cases treated. Furthermore, as a *curative* the result of this treatment (G) presented a striking contrast to that of the previous one (F), only 12·5 per cent. of cases relapsing within the post-treatment observation period of sixty days.

**COMPARISON OF RESULTS OBTAINED FROM THE  
VARIOUS TREATMENTS**

PALLIATIVE

From the figures relating to series C, D and E it will be seen that there is no evidence that small doses of arsenic (minims 15 daily) in combination with quinine are more efficacious than the same dose of quinine alone. There is also no evidence that a combination of small doses of arsenic and strychnine with quinine is more efficacious than quinine alone.

From the figures relating to F and G it will be seen that Liquor arsenicalis alone in large doses (minims 30 daily for eight weeks) effectively controls the febrile relapses; but if reliance were placed solely upon febrile attacks as indicating infection a fallacious

TABLE XII.

Comparison of palliative results obtained from the different treatments.

	C	D	E	F	G
	Liquor arsenici HCl minims 15 + Quinine HCl grains 5 daily for 8 weeks	Liquor arsenici HCl minims 15 and Liquor strychninae HCl minims 15 + Quinine HCl grains 5 daily for 8 weeks	Quinine HCl grains 5 daily for 8 weeks	Liquor arsenicalis minims 30 daily with one or two intermissions, for 8 weeks	Liquor arsenicalis minims 30 daily with two periods of intermission for 8 weeks + Quinine 2 HCl grains 15 intramuscularly on each of the first two days only
Number of cases treated	28	25	26	14	33
Percentage of parasitic febrile relapse cases per cases treated (average per week) ... ..	25.7	13.2	17.0	3.8	2.7
Percentage of all febrile (parasitic and non-parasitic) cases per cases treated (average per week) ... ..	32.0	20.3	19.0	7.3	8.7
Percentage of all parasitic (febrile and non-febrile) cases per cases treated (average per week) ... ..	42.4	37.6	46.3	28.1	3.9

TABLE XIII.

Comparison of curative results obtained from the different treatments.

Series	Treatment	Number of cases observed after treatment*	Number of cases which relapsed within 60 days*	Number of cases not relapsing but observed for less than 60 days	Percentage of cases which relapsed	
					Minimum	Maximum
A	Liquor arsenicalis, minims 15 daily ... ..	3	3	...	100.0	100.0
B	Liquor arsenicalis minims 15 daily for 8 weeks + Quinine 2 HCl grains 15 intramuscularly, on each of the first two days only ...	2	2	...	100.0	100.0
C	Liquor arsenici HCl minims 15 + Quinine HCl grains 5 daily for 8 weeks ... ..	28	23	1	82.0	86.0
D	Liquor arsenici HCl minims 15 and Liquor strychninae HCl minims 15 + Quinine HCl grains 5 daily for 8 weeks ... ..	24	18	2	75.0	83.0
E	Quinine HCl grains 5 daily for 8 weeks ... ..	26	16	2	62.0	69.0
F	Liquor arsenicalis, minims 30 daily, with one or two periods of intermission, for 8 weeks ... ..	13	11	...	85.0	85.0
G	Liquor arsenicalis, minims 30 daily, with two periods of intermission, for 8 weeks + Quinine 2 HCl grains 15 intramuscularly on each of the first two days only ... ..	32	4	...	12.5	12.5
H	Quinine 2 HCl grains 15 intramuscularly on each of two consecutive days only ... ..	30	21	...	70.0	70.0

\* Including those cases in which treatment was abandoned as the condition was uncontrolled.

estimate of its efficacy would be obtained, for Table XII shows that whereas the figure in series F for parasitic febrile relapse cases is 3·8 per cent., that of all parasitic relapse cases, both febrile and non-febrile, is 28·1 per cent. Arsenic in large doses, then, is anti-periodic in the sense that it controls the fever, but its control over parasites is much less. Further, the combination of quinine and arsenic in large doses is superior to arsenic alone, the total number of parasitic relapse cases being 3·9 per cent. for the combination and 28·1 per cent. for arsenic alone. Expressed in clinical terms, the combination of large doses of arsenic and quinine controls the patients' fever and renders their blood negative during the course of treatment to an extent that arsenic alone is incapable of effecting.

#### CURATIVE

It will be seen in Table XIII that there is little to choose between any of the treatments with the exception of G, which is a combination of large doses of arsenic with quinine. This treatment gave only 12·5 per cent. of relapses within the sixty-day post treatment observation period.

TABLE XIV.

## C. Results of oral administration of Liquor arsenici HCl minus 15 + Quinine HCl grains 5 daily for 8 weeks, in simple tertian malaria.

† E.A. = East Africa.

M. = Mesopotamia.

S. = Salonika.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases in which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1191	S.	12	4	4	6.9.18	Same day	1-2	P <sub>2</sub>	○	P <sub>3</sub>	1*	○	○	1 + P <sub>3</sub>	1 + P <sub>3</sub>	6	...	101° F. on 5th, 100° F. on 8th, 103° F. on 12th, 100° F. on 17th days; 101° F. on 18th, 103° F. on 19th, 104.5° F. on 24th days.	
1192	S.	20	7	6	6.9.18	2	3	○	○	○	○	○	1*	○	○	34-37	37	...	
1193	S.	24	4	4	6.9.18	1	3	1*	○	○	2*	○	1*	1*	2*	13	19	...	
1194	S.	18	4	4	9.9.18	1	...	P <sub>3</sub>	2 + P <sub>5</sub>	2 + P <sub>2</sub>	3 + P <sub>2</sub>	○	○	1 + P <sub>2</sub>	5 + P <sub>2</sub>	1	7	...	
1195	S.	16	6	4	12.9.18	3	5	P <sub>1</sub>	○	○	○	○	○	○	○	...	...	37	
1196	S.	24	4	3	12.9.18	4	5	P <sub>1</sub>	○	○	○	○	○	○	○	15	16	...	
1197	S.	12	4	3	13.9.18	3	...	P <sub>2</sub>	2 + P <sub>2</sub>	P <sub>6</sub>	1*	○	1 + P <sub>1</sub>	3 + P <sub>3</sub>	P <sub>1</sub>	1	3	...	
1198	S.	23	4	4	13.9.18	2	4	○	○	1*	2*	1*	1 + P <sub>1</sub>	1 + P <sub>2</sub>	1	6	3	...	
1199	S.	15	4	4	17.9.18	3	7	P <sub>1</sub>	○	○	P <sub>1</sub>	P <sub>1</sub>	P <sub>3</sub>	P <sub>7</sub>	P <sub>1</sub>	1	2	...	
1200	E.A.	26	19	15	18.9.18	2	3	○	○	○	○	2 + P <sub>1</sub>	○	1	3 + P <sub>2</sub>	1	2	...	
1201	S.	26	15	15	19.9.18	Same day	1	○	○	○	2*	○	○	2	P <sub>2</sub>	5	...	Quinine orally grs. 30 on 11th day.	
1202	S.	15	3	3	20.9.18	2	3	○	○	1*	○	○	○	○	○	...	...	64	

† Three days after commencement of treatment are allowed for the disappearance of parasites and for the fall of the temperature to normal; consequently, the records for the first week refer to the last three days only of that week.

TABLE XIV—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment							Parasite relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) in — days after cessation of treatment	Observation period (in days) in cases in which relapse did not occur	Remarks
								1st	2nd	3rd	4th	5th	6th	7th	8th			
1203	S.	26	4	4	23.9.18	2	4	0	0	0	0	0	P <sub>3</sub>	P <sub>5</sub>	P <sub>1</sub>	5	...	100° F. on 1st, 3rd and 5th days; 103.8° F. on 7th day.
1204	S.	17	12	6	24.9.18	2	5	P <sub>1</sub>	0	0	0	0	1*	0	3*	11-12	11	...
1205	S.	11	2	2	30.9.18	2	2	0	0	0	0	0	0	0	0	...	...	68
1206	E.A.	28	4	2	4.10.18	2	...	1 + P <sub>2</sub>	2 + P <sub>5</sub>	2 + P <sub>6</sub>	2 + P <sub>6</sub>	1 + P <sub>6</sub>	P <sub>7</sub>	3 + P <sub>4</sub>	2 + P <sub>6</sub>	1	1	...
1207	S.	25	5	4	9.10.18	2	5	P <sub>1</sub>	0	0	0	0	0	0	0	1*	...	66
1208	S.	2	4	3	15.10.18	3	4	0	0	0	0	1*	0	0	0	0	...	100° F. on 5th and 8th days; 100.4° F. on 19th day, 100° F. on 22nd day.
1209	S.	26	3	3	17.10.18	4	...	P <sub>3</sub>	2 + P <sub>4</sub>	P <sub>7</sub>	1 + P <sub>6</sub>	P <sub>7</sub>	4 + P <sub>3</sub>	1 + P <sub>3</sub>	P <sub>6</sub>	18	17	Quinine orally grs. 30 on 15th day
1210	S.	13	7	6	17.10.18	2	...	P <sub>2</sub>	P <sub>3</sub>	1 + P <sub>6</sub>	P <sub>2</sub>	P <sub>2</sub>	3	P <sub>1</sub>	P <sub>4</sub>	11	13	Pneumonia on cessation of treatment.
1211	S.	27	5	5	18.10.18	Apyrexia	2	0	1 + P <sub>6</sub>	P <sub>1</sub>	P <sub>6</sub>	1	1	1 + P <sub>2</sub>	P <sub>1</sub>	9	...	Quinine orally grs. 30 on 11th day
1212	S.	28	6	4	18.10.18	1	2	0	0	0	0	0	0	0	0	...	...	Bronchial pneumonia on cessation of treatment.
1213	M.	40	4	3	21.10.18	Same day	2	0	0	1*	P <sub>1</sub>	P <sub>5</sub>	1*	P <sub>2</sub>	2*	11	...	Quinine orally grs. 30 on 13th day
1214	...	...	...	...	13.10.18	5	...	P <sub>2</sub>	2 + P <sub>6</sub>	1 + P <sub>6</sub>	P <sub>1</sub>	3	7	7	...	...	...	Treatment changed: condition uncon- trolled.
1215	S.	25	4	3	11.9.18	2	4	0	0	0	0	0	P <sub>2</sub>	2 + P <sub>3</sub>	...	...	...	Quinine intramuscularly in 8th week.
1216	S.	11	6	5	30.8.18	2	6	P <sub>2</sub>	0	1*	4 + P <sub>2</sub>	2 + P <sub>5</sub>	1 + P <sub>5</sub>	...	...	...	...	Quinine intramuscularly in 7th week.
1217	S.	3	4	3	10.9.18	Apyrexia	2	0	0	0	2 + P <sub>6</sub>	...	...	...	...	...	...	Quinine intramuscularly in 5th week.
1218	S.	15	5	4	10.9.18	4	...	P <sub>2</sub>	P <sub>4</sub>	2 + P <sub>6</sub>	2 + P <sub>6</sub>	...	...	...	...	...	...	Quinine intramuscularly in 5th week.

TABLE XV.

**D. Results of oral administration of Liquor arsenici HCl minims 15 + Quinine HCl grains 5 daily for 8 weeks, in simple tertian malaria.**

† E. = Egypt. E.A. = East Africa. S. = Salonika.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse (above 100° F.) occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1219	S.	24	5	4	7.9.18	Apyrexia	1	0	0	0	0	0	0	0	9	12	...	Not observed after treatment. Quinine intramuscularly on 1st day.	
1220	S.	15	4	4	7.9.18	2	2	0	0	0	0	0	0	0	...	...	...		
1221	E.A.	10	4	3	8.9.18	4	7	† P <sub>3</sub>	P <sub>1</sub>	P <sub>1</sub>	P <sub>2</sub>	2 + P <sub>2</sub>	1 + P <sub>5</sub>	1 + P <sub>6</sub>	P <sub>7</sub>	1	...	...	
1222	E.A.	13	8	6	8.9.18	8	...	3	1 + P <sub>6</sub>	P <sub>2</sub>	P <sub>2</sub>	P <sub>2</sub>	0	0	0	10	10	...	
1223	S.	20	4	4	8.9.18	1	4	0	P <sub>1</sub>	P <sub>2</sub>	0	0	0	0	...	...	42		
1224	S.	14	4	3	9.9.18	4	4	1*	P <sub>1</sub>	0	0	0	0	P <sub>1</sub>	0	7	8	...	
1225	S.	16	4	3	11.9.18	2	4	P <sub>1</sub>	0	0	P <sub>2</sub>	P <sub>2</sub>	0	P <sub>1</sub>	0	1	...	Quinine orally grs. 45 on 21st day.	
1226	S.	12	7	6	12.9.18	6	6	2	1*	0	1 + P <sub>2</sub>	3	1 + P <sub>2</sub>	P <sub>3</sub>	1 + P <sub>6</sub>	1	14	...	
1227	S.	14	8	8	12.9.18	Same day	5	P <sub>1</sub>	0	0	0	0	0	0	...	...	...	38	
1228	S.	13	4	3	17.9.18	2	2	0	0	0	0	0	0	0	1*	...	...	69	100.8° F. on 35th day.
1229	S.	14	4	3	17.9.18	3	5	P <sub>1</sub>	P <sub>2</sub>	0	0	0	0	0	P <sub>1</sub>	3	10	...	

\* Three days after commencement of treatment are allowed for the disappearance of parasites and for the fall of the temperature to normal; consequently, the records for the first week refer to the last three days only of that week.

TABLE XV. *continued.*

Number of case	Place of infection	Interval (in months) between admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in—days after cessation of treatment	Febrile relapse (above 100° F.) occurred in—days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1230	S.	15	4	4	20.9.18	5	+	0	2*	1	0	2 + P <sub>2</sub>	1 + P <sub>5</sub>	0	3*	11	14	...	100° F. on 3rd, 5th and 7th days.
1231	S.	12	8	8	20.9.18	—	7	3	1*	0	0	0	1*	0	0	8	8	...	
1232	S.	24	8	7	22.9.18	2	2	0	0	0	0	0	0	0	0	...	...	66	
1233	S.	13	3	2	24.9.18	3	4	0	0	0	0	0	P <sub>5</sub>	P <sub>4</sub>	P <sub>6</sub>	1	...	...	Colloidal manganese on 3rd day.
1234	S.	15	7	5	27.9.18	2	2	0	0	1*	0	0	P <sub>1</sub>	0	0	8	7	...	
1235	S.	15	5	5	4.10.18	1	3	0	0	0	0	0	0	0	0	26	27	...	
1236	S.	11	5	4	9.10.18	1	1	0	0	0	0	0	0	0	0	19	...	...	Quinine orally grs. 45 on 20th day.
1237	E.	2	5	3	18.10.18	2	4	0	0	0	0	0	0	4*	5*	...	...	63	Influenza in 7th, pneumonia in 8th weeks.†
1238	S.	16	9	9	18.10.18	1	2	0	3 + P <sub>3</sub>	P <sub>3</sub>	2 + P <sub>5</sub>	1 + P <sub>4</sub>	1	P <sub>5</sub>	P <sub>6</sub>	1	...	...	Quinine orally grs. 30 on 7th day.
1239	S.	28	7	6	23.10.18	1	7	P <sub>3</sub>	P <sub>3</sub>	P <sub>2</sub>	P <sub>7</sub>	P <sub>2</sub>	0	P <sub>4</sub>	3	...	...	77	Bronchial pneumonia on cessation of treatment.
1240	S.	10	2	2	24.10.18	Apyrexia	2	0	0	1*	1*	2*	P <sub>3</sub>	P <sub>1</sub>	0	5	5	...	Quinine orally grs. 15 on 10th day
1241	S.	...	...	...	24.10.18	Apyrexia	...	1	P <sub>7</sub>	P <sub>6</sub>	3	2	0	P <sub>7</sub>	P <sub>2</sub>	1	...	...	Quinine orally grs. 30 on 7th day
1242	S.	23	5	4	28.10.18	Apyrexia	...	P <sub>1</sub>	1 + P <sub>4</sub>	P <sub>2</sub>	P <sub>6</sub>	P <sub>7</sub>	P <sub>1</sub>	P <sub>2</sub>	P <sub>1</sub>	7	...	...	Quinine intramuscularly in 6th week.
1243	E.A.	13	7	1	11.9.18	2	...	1 + P <sub>1</sub>	P <sub>3</sub>	1 + P <sub>6</sub>	P <sub>7</sub>	4 + P <sub>3</sub>	...	...	...	...	...	...	

† During treatment.



TABLE XVI.  
E. Results of oral administration of Quinine HCl grains 5 daily for 8 weeks, in simple tertian malaria.

† E. Egypt. E.A. West Africa. S. Salonika.

Number of case	Place of infection	Interval (in months) between admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days after cessation of treatment	Observation period (in days) in cases in which relapse did not occur
								Week of Treatment										
								1st	2nd	3rd	4th	5th	6th	7th	8th			
1244	S.	23	6	6	4-9-18	2	...	† P <sub>3</sub>	4 + P <sub>2</sub>	2 + P <sub>3</sub>	1 + P <sub>4</sub>	1 + P <sub>4</sub>	P <sub>7</sub>	1 + P <sub>5</sub>	P <sub>5</sub>	1	8	...
1245	E.A.	9	5	3	7-9-18	1	...	P <sub>3</sub>	1 + P <sub>6</sub>	P <sub>6</sub>	2 + P <sub>1</sub>	P <sub>7</sub>	P <sub>4</sub>	0	1 + P <sub>2</sub>	1	19	...
1246	S.	12	4	4	9-9-18	2	3	0	0	1*	0	0	0	0	0	...	...	23
1247	S.	24	4	3	12-9-18	1	3	0	0	0	0	0	0	0	3*	...	...	84
1248	S.	15	4	4	15-9-18	2	3	0	1	1 + P <sub>4</sub>	1 + P <sub>4</sub>	1 + P <sub>3</sub>	P <sub>1</sub>	2 + P <sub>2</sub>	P <sub>2</sub>	13	...	...
1249	S.	13	6	6	25-9-18	2	...	P <sub>3</sub>	1 + P <sub>3</sub>	2 + P <sub>5</sub>	P <sub>5</sub>	P <sub>6</sub>	P <sub>7</sub>	P <sub>4</sub>	P <sub>5</sub>	1	...	...
1250	S.	11	5	4	25-9-18	1	10	P <sub>3</sub>	P <sub>3</sub>	0	0	0	P <sub>1</sub>	0	0	15	...	...
1251	S.	3	4	3	25-9-18	1	2	0	0	0	0	0	0	0	0	...	...	86
1252	E.	37	4	3	25-9-18	Same day	...	1 + P <sub>2</sub>	P <sub>6</sub>	P <sub>5</sub>	1 + P <sub>4</sub>	P <sub>4</sub>	P <sub>3</sub>	2 + P <sub>5</sub>	P <sub>2</sub>	1	...	...
1253	S.	4	3	2	25-9-18	1	2	0	0	P <sub>2</sub>	P <sub>2</sub>	0	P <sub>4</sub>	P <sub>3</sub>	1	2	1	...
1254	S.	13	4	3	26-9-18	1	3	0	0	0	0	1*	0	0	0	...	...	79

101.2° F. on 2nd day (bronchitis); 100° F. on 40th day.  
100° F. on 26th and 35th days.  
Colloidal manganese on 2nd day.  
Quinine orally on 23rd day.  
Colloidal manganese on 2nd day.

\* Three days after commencement of treatment are allowed for the disappearance of parasites and for the fall of the temperature to normal; consequently, the records for the first week refer to the last three days only of that week.

TABLE XVI—continued.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in—days after cessation of treatment	Febrile relapse (above 100° F.) occurred in—days in—cases after cessation of treatment	Observation period (in days) in which relapse did not occur	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1255	S.	24	3	2	26.9.18	1	2	0	0	0	0	0	0	...	...	40	Quinine orally grs. 30 on 35th day.		
1256	S.	14	6	4	26.9.18	1	2	0	P <sub>1</sub>	0	0	P <sub>1</sub>	P <sub>1</sub>	...	...	...			
1257	S.	23	6	5	27.9.18	2	5	P <sub>1</sub>	0	0	0	0	0	...	...	65	Quinine orally grs. 45 on 15th day.		
1258	S.	21	8	7	27.9.18	3	...	P <sub>1</sub> 2 + P <sub>2</sub>	P <sub>6</sub>	P <sub>6</sub>	P <sub>6</sub>	P <sub>7</sub>	P <sub>3</sub> 0	15	...	...			
1259	S.	13	4	3	29.9.18	2	2-3	0	1	P <sub>3</sub>	0	1 + P <sub>3</sub> 1	P <sub>3</sub> 1	15	15	...	Quinine orally grs. 45 on 15th day.		
1260	S.	28	8	7	1.10.18	Same day	2	0	0	0	0	0	0	...	...	79			
1261	S.	27	5	5	13.10.18	2	2	0	1 + P <sub>3</sub>	P <sub>4</sub>	P <sub>3</sub> 1	P <sub>2</sub>	P <sub>2</sub>	4	5	...	No febrile relapse in 77 days. Quinine orally grs. 30 on 12th day		
1262	E.A.	16	10	7	14.10.18	3	...	P <sub>3</sub>	1 + P <sub>6</sub>	1 + P <sub>2</sub>	P <sub>2</sub> 1 + P <sub>6</sub>	P <sub>7</sub>	P <sub>6</sub>	1	9	...		Quinine orally grs. 30 on 7th day. Treatment changed.	
1263	S.	24	4	4	14.10.18	2	3	0	0	0	0	0	0	...	...	99	Quinine orally grs. 30 on 12th day.		
1264	S.	28	5	5	18.10.18	Same day	1	0	0	0	0	0	0	...	...	61		Quinine orally grs. 30 on 7th day.	
1265	S.	6	5	4	21.10.18	1	5	P <sub>1</sub>	0	0	0	P <sub>4</sub>	0	1	...	...	Treatment changed.		
1266	S.	28	5	5	21.10.18	2	...	P <sub>3</sub> 2 + P <sub>6</sub> 2	1	1 + P <sub>3</sub>	0	P <sub>1</sub>	0	2	...	...		Meades in 1st week.	
1267	S.	15	5	5	22.10.18	1	3	0	0	0	P <sub>3</sub> 2 + P <sub>6</sub>	P <sub>6</sub> 2 + P <sub>4</sub>	P <sub>6</sub>	1	...	...	Meades in 1st week.		
1268	S.	27	4	3	22.9.18	Same day	...	P <sub>3</sub>	P <sub>7</sub>	P <sub>6</sub>	P <sub>6</sub>	P <sub>6</sub>	...	...	...	...		Meades in 1st week.	
1269	S.	14	4	4	17.9.18	Same day	1	0	0	0	0	...	...	...	...	84			

F. Results of oral administration of *Liquor arsenicalis* minims 30 daily, with one or two intermissions, for 8 weeks, in simple tertian malaria.

† E.A. = East Africa. S. = Salonika.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in—days after cessation of treatment	Febrile relapse (above 100° F.) occurred in—days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1270	S.	12	3	3	21.8.18	Same day	3	○	○	○	○	○	○	P <sub>1</sub>	P <sub>1</sub>	11	29	...	(post-treatment) 100.4° F. on 6th, 100° F. on 7th days. Influenza first 2 weeks. §
1271	E.A.	9	6	2	24.8.18	10	5	+2* 3*	○	○	○	○	○	○	○	11	16	...	
1272	S.	15	3	3	24.8.18	2	5	P <sub>1</sub>	○	○	○	○	○	○	○	...	...	103	100.4° F. on 4th, 100° F. on 58th, 61st and 66th days.
1273	S.	26	3	2	26.8.18	Same day	2	○	○	○	○	○	○	○	○	...	...	66	
1274	S.	15	3	3	26.8.18	2	5	P <sub>1</sub>	○	○	○	○	○	○	○	...	...	...	Not observed.
1275	S.	12	3	3	27.8.18	4	6	P <sub>2</sub>	○	○	○	○	○	○	1 + P <sub>5</sub>	1	1	...	
1276	S.	13	3	2	28.8.18	1	6	P <sub>2</sub>	P <sub>1</sub> + P <sub>1</sub>	○	○	○	○	○	○	3	11	...	
1277	S.	11	7	7	28.8.18	5	3	○	○	○	○	○	P <sub>1</sub>	P <sub>2</sub>	○	15	42	...	
1278	S.	12	5	5	29.8.18	4	...	P <sub>3</sub>	P <sub>1</sub>	P <sub>1</sub>	P <sub>7</sub>	P <sub>5</sub> + P <sub>1</sub>	P <sub>5</sub>	P <sub>6</sub>	P <sub>5</sub>	5	8	...	No febrile relapse in 44 days.
1279	S.	12	3	3	4.9.18	1	4	○	○	○	○	○	○	P <sub>1</sub>	P <sub>1</sub>	13	...	...	
1280	S.	24	4	3	16.9.18	3	5	P <sub>1</sub>	○	○	○	P <sub>1</sub> + P <sub>5</sub>	P <sub>5</sub>	P <sub>5</sub>	P <sub>7</sub>	1	10	...	
1281	E.A.	21	8	6	28.9.18	Apixenia	3	P <sub>1</sub>	○	○	○	○	○	○	○	39	39	...	Symptoms of arsenical poisoning. Discharged on 8th day.
1282	S.	23	1	1	30.7.18	2	4	P <sub>2</sub>	P <sub>3</sub>	○	○	○	P <sub>3</sub>	...	...	8	...	...	Treatment stopped owing to total but temporary blindness. No febrile relapse in 62 days but parasites present daily.
1283	S.	14	2	2	12.8.18	3	6	P <sub>2</sub>	○	1*	4*	○	○	...	...	8	...	...	

§ Three days after commencement of treatment are allowed for the disappearance of parasites and for the fall of the temperature to normal; consequently, the records for the first week refer to the last three days only of that week. \* During treatment.

## TABLE XVIII.

**G.** Results of administration of Liquor arseniculi minimi 30 daily, with two periods of intermission, for 8 weeks of Quinine 2 HCl grains 15 intramuscularly on each of the first two days only, in simple tertian malaria.

E. = Egypt. E.A. = East Africa. S. = Salonika.

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in — days after cessation of treatment	Febrile relapse (above 100° F.) occurred in — days in cases which cessation did not of relapse treatment	Remarks
								Week of Treatment										
								1st	2nd	3rd	4th	5th	6th	7th	8th			
1284	S.	23	3	3	4-9-18	1	2	0	0	0	0	0	0	0	...	65	Symptoms of arsenical poisoning.†	
1285	S.	24	4	4	5-6-18	1	1	0	0	0	0	0	0	0	...	71		
1286	S.	14	4	4	5-6-18	1	2	0	0	0	0	0	0	0	...	69	100° F. on 33rd day	
1287	S.	25	4	3	5-9-18	Apyrexia	1	0	0	0	P <sub>1</sub>	0	0	0	...	137		
1288	S.	14	5	4	8-9-18	1	2	0	0	0	0	0	0	0	...	67	100° F. on 55th day.	
1289	S.	16	8	7	12-9-18	1	1	0	1*	P <sub>2</sub>	4 + P <sub>3</sub>	1 + P <sub>3</sub>	1 + P <sub>3</sub>	P <sub>0</sub>	19	...		
1290	S.	25	4	4	14-9-18	Apyrexia	1	0	0	0	0	0	0	0	...	72		
1291	E.A.	9	7	5	17-9-18	Same day	2	0	0	0	0	0	0	0	...	69	102° F. on 13th day.	
1292	S.	18	12	3	19-9-18	Same day	2	0	0	0	0	0	0	0	...	...	Not observed: died of pneumonia.	
1293	S.	10	4	3	20-9-18	1	4	0	0	0	0	0	1	3 + P <sub>1</sub>	1	...		
1294	S.	24	4	3	20-9-18	1	1	0	0	2*	0	0	0	0	...	71	Temperature in 4th week due to catarrhal cold.	
1295	S.	27	3	3	23-9-18	1	3	0	0	0	0	0	0	0	...	70	103° F. on 10th day.	
1296	S.	22	4	3	24-9-18	1	2	0	0	0	0	0	0	0	...	70	100° F. on 15th and 17th days.	
1297	S.	15	4	3	24-9-18	Apyrexia	2	0	0	0	0	0	0	0	...	63		
1298	S.	16	4	4	26-9-18	1	2	0	0	0	0	0	0	1*	...	64	100° F. on 23rd day.	

† During treatment.

TABLE XVIII—continued

Number of case	Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Number of febrile paroxysms (parasitic and non-parasitic) and results of blood examinations during treatment								Parasitic relapse occurred in—days after cessation of treatment	Febrile relapse (above 100° F.) occurred in—days after cessation of treatment	Observation period (in days) in cases which did not relapse	Remarks
								Week of Treatment											
								1st	2nd	3rd	4th	5th	6th	7th	8th				
1299	S.	21	4	4	31.9.18	1	2	0	0	0	0	0	0	0	1*	...	...	100	101.6° F. on 12th day (bronchial catarrh).
1300	E.A.	13	9	4	2.10.18	1	2	0	0	1*	0	0	0	0	0	...	...	117	
1301	E.	16	5	5	10.10.18	Same day	1	0	0	0	0	0	0	0	0	...	...	67	
1302	S.	18	10	4	13.10.18	1	2	0	0	0	0	0	0	0	0	...	...	69	
1303	E.A.	27	8	6	16.10.18	1	1	0	0	1*	0	0	0	0	0	...	...	76	
1304	S.	24	6	4	16.10.18	1	2	0	0	0	0	3*	0	0	0	...	...	104	
1305	S.	15	2	2	21.10.18	1	3	0	0	0	0	0	0	0	0	...	...	125	
1306	S.	15	5	5	22.10.18	1	2	0	0	0	1*	0	2*	0	0	...	...	98	
1307	S.	2	4	4	22.10.18	1	3	0	0	5*	0	0	0	0	0	...	...	60	Influenza in 3rd week.†
1308	S.	28	10	9	23.10.18	Apixia	1	0	0	0	0	0	0	0	0	...	...	96	
1309	S.	15	3	2	23.10.18	Apixia	1	0	0	0	0	0	1*	0	0	...	...	112	
1310	S.	16	3	2	24.10.18	2	2	0	0	0	0	0	0	0	0	...	...	66	
1311	S.	16	5	5	24.10.18	1	2	0	0	0	0	0	0	0	0	...	...	60	
1312	S.	16	4	3	25.10.18	1	3	0	0	0	0	0	0	0	0	...	...	94	
1313	E.A.	8	4	2	26.10.18	2	3	0	0	0	0	0	2*	2	1*	15	16	...	Influenza in 6th and 7th weeks.† Symptoms of arsenical poisoning.† Treatment changed.
1314	S.	30	3	2	24.8.18	Same day	2	0	1*	0	0	0	0	0	0	...	...	93	
1315	E.A.	10	7	3	27.9.18	1	3	0	1*	0	0	0	0	1 + P <sub>g</sub>	...	...	...		
1316	E.A.	7	7	1	8.9.18	1	2	0	0	...	...	...	...	...	...	...	...	60	104° F. on 9th day.

† During treatment.

TABLE XIX.

H. Results of administration of Quinine 2 HCl grains 15 intramuscularly on each of two consecutive days only, in simple tertian malaria

\* E.A. = East Africa. F. = France. It. = Italy. S. = Salonika.

Number of case	*Place of infection	Interval (in months) between first admission to a hospital with malaria and present treatment	Interval (in months) between leaving infected area and present treatment	Interval (in months) between arrival in England and present treatment	Date of end of treatment	Temperature fell to normal in — days after first dose	Parasites disappeared from cutaneous blood in — days after first dose	Parasitic relapse occurred in — days after last dose	Febrile relapse (above 100°F.) occurred in — days after last dose	Observation period (in days) in cases which did not relapse	Remarks
1317	S.	11	2	1	25.6.18	Apyrexia	2	18	18	...	
1318	S.	13	5	4	25.6.18	1	3	15	21	...	
1319	S.	9	3	2	25.6.18	1	4	22	22	...	
1320	S.	12	3	2	5.7.18	1	2	15	18	...	100°F. on 8th day
1321	S.	23	2	2	6.7.18	Same day	1	...	...	87	Irregular temperature after treatment. <i>Vide</i> chart.
1322	S.	22	2	1	6.7.18	Same day	1	12	15	...	
1323	S.	1	2	1	6.7.18	3	1	23	24	...	
1324	S.	9	2	2	7.7.18	Same day	1	11	13	...	
1325	S.	9	3	2	9.7.18	Same day	2	19	22	...	
1326	S.	27	10	1	11.7.18	1	1	14	22	...	
1327	S.	23	10	1	12.7.18	1	1	18	22	...	
1328	S.	16	10	1	12.7.18	1	2	12	13	...	
1329	S.	25	2	2	14.7.18	...	2	25	...	...	
1330	It.	13	0	0	22.7.18	1	2	10	14	...	
1331	S.	26	9	2	23.7.18	1	2	17	19	...	
1332	S.	11	2	1	25.7.18	Apyrexia	2	...	...	92	
1333	S.	10	2	1	27.7.18	Apyrexia	2	...	...	66	
1334	S.	11	7	6	27.7.18	1	2	...	...	73	101°F. on 24th day
1335	S.	12	4	3	28.7.18	Same day	2	...	...	73	
1336	S.	23	4	2	28.7.18	Same day	1	...	...	68	100°F. on 34th day
1337	E.A.	16	7	4	28.7.18	2	3	13	15	...	
1338	S.	21	6	5	28.7.18	2	2	20	21	...	
1339	S.	9	5	4	28.7.18	1	1	...	...	65	
1340	S.	15	6	5	28.7.18	1	2	16	15	...	
1341	E.A.	8	5	1	31.7.18	Same day	3	6	9	...	
1342	F.	2	2	2	8.8.18	Same day	3	23	25	...	
1343	S.	...	...	...	14.8.18	1	3	...	...	71	
1344	S.	24	3	3	22.8.18	1	1	21	24	...	
1345	S.	12	2	1	23.8.18	1	2	20	22	...	
1346	S.	...	...	...	23.8.18	1	1	...	...	62	100°F. on 18th, 24th and 25th days.

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